MAR 30 1920

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice
Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917. Authorized on July 3, 1918.

Vol. XXXI—No. 348] BALTIMORE, FEBRUARY, 1920 [Price, 50 Cents

CONTENTS

PAGE

Experimental Pneumectomy. (Illustrated.)
By George J. Heuer and George R. Dunn 31

The Effect of Arteriovenous Fistula Upon the Heart and Blood-Vessels. An Experimental and Clinical Study. (Illustrated.)
By Mont R. Reid 43

PAGE

The Biological Classification of Influenza Bacilli. (Illustrated.)
By T. M. Rivers, M. D. 50

Titles of Papers Appearing During the Year, Elsewhere than in the Bulletin, by Present and Former Members of the Hospital and Medical School Staff 54

EXPERIMENTAL PNEUMECTOMY

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AND

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(From The Hunterian Laboratory of Experimental Surgery)

In the course of some experiments relating to thoracic surgery, carried on with many interruptions during the past six years by Drs. Henry Cave, E. Holman and ourselves, we have had occasion to remove the entire lung from 23 dogs. It seemed to us of interest to assemble the results obtained and to study them from various viewpoints: namely, (1) to discover the effects of total pneumectomy upon the pulse, blood pressure, and respiration; (2) to determine the results obtained in the treatment of the bronchial stump by various methods; (3) to observe the reaction on the part of the pleura upon the pneumectomized side—meaning by reaction the development or the absence of a pleural effusion; (4) to follow the fate of the intrapleural cavity resulting after removal of the lung and the methods of its obliteration; (5) to observe the reaction on the part of the remaining lung—by reaction meaning the development or absence of a simple enlargement associated with dilatation of the alveoli analogous to emphysema, or of a hypertrophy or of a hyperplasia; and (6) to estimate the probable duration of life in animals after a total pneumectomy. These various aspects of the subject are of predominant importance in lobectomy in man. They have been the subject of previous experimental work, but agreement in the results are often lacking. The results of our experiments should serve to clarify some of the mooted points.

The technic employed was quite uniformly as follows: (a) Intratracheal anesthesia with a positive pressure apparatus was always used. (b) In view of the infectious complications following previous experimental work, the skin was cleaned with the greatest care. After shaving and washing with soap and water, it was washed with alcohol and dried; then was washed with pure carbolic acid followed in a moment by alcohol. If the original scrubbing of the skin is not so vigorous as to cause multiple bleeding points, the skin does not suffer from this vigorous treatment and it was rare that even the slightest dermatitis followed it.[1] (c) An intercostal incision was made upon the left side, preferably in the fourth or fifth interspace. The chest was opened widely and the wound held apart with a rib spreader. The lung was drawn into the wound, the pulmonary arteries and veins at the hilus were individually isolated, doubly ligated with silk, and divided. The main bronchus or its main branches were isolated and stripped of all lung tissue. The lung was then removed, after the division of the naked bronchi. The divided bronchi were closed by the various methods to be subsequently described.

[1] The same technic has been used in human subjects; but here great care must be exercised not to allow the carbolic acid to run down over the skin; otherwise, an annoying dermatitis will result.

Before closure a culture was usually made from the mucous membrane just below the bifurcation of the trachea, in order to determine the bacterial flora in the upper air passages of the dog. The closed bronchial stump was dropped back into the pleural cavity, with no attempt to cover it with a fold of the pleura or pericardium. The wound was closed in layers with silk without drainage, the two ribs adjacent to the incision being brought together with encircling sutures. A simple collodion dressing was used to cover the skin incision. Before closure of the thoracic wall, the remaining lung was distended to its normal capacity.

Summary of Results.—In 23 dogs in which total pneumectomy was practised, there were 13 recoveries and 10 deaths. The fatalities occurred in from four days to two months after operation. Six of the deaths were due to an epidemic of distemper which swept through the kennels during the earlier period of our experimental work. The autopsy examinations in this group do not show a single instance of infection of the parietal wound or pleura or leakage from the bronchial stump.[2] One animal died of a simple pneumonia unassociated with other evidences of distemper. At autopsy there was no infection of the parietal wound or pleura or leakage from the bronchial stump. One animal died apparently from starvation, two months after operation. At autopsy there was a remarkable degree of emaciation, but no other assignable cause for death. There was no infection of the parietal wound or pleura or any leakage from the bronchial stump. Two animals died of acute pneumothorax, the result of leakage from the bronchial stump. In one of these the failure to secure an adequate closure of the bronchial stump was intentional. In the other a necrosis of the bronchial wall followed the application of an intentionally flattened (not rolled) metal band. These cases will be further discussed under the treatment of the bronchial stump.

The animals were kept under observation for intervals varying from several days to over one year. They were studied fluoroscopically from the day of operation onward, in order to determine (a) the presence of fluid in the pleural cavity from which the lung had been removed; (b) the position and movements of the diaphragm[3] upon the pneumectomized side as compared with the contralateral side; and (c) the mode of obliteration of the cavity left after the removal of the lung. When the animal was sacrificed, the thoracic organs were fixed *in situ* with the greatest possible care. The animals were anesthetized, placed in exactly the dorsal position; and, while being bled from the femoral artery, a 10 per cent formalin solution, introduced under low pressure into the vein, was carried throughout the circulation by cardiac action. At approximately the last respiratory effort a clamp was placed across the isolated trachea, and the body allowed to harden for several hours. The animals invariably died without a struggle. The illustrations in the paper are reproductions of photographs of dissections made upon animals fixed in this way.

Technic of Lung Excision.—Total lung excision is a very simple procedure in the dog. Through a properly placed intercostal incision the entire lung can readily be delivered, the larger vessels at the hilus isolated, doubly ligated and divided, and the main bronchus freed for a distance of several centimeters. The comparatively long bronchial stump lends itself readily to any one of a number of methods of closure, all of which if carefully done will ensure the air-tight closure and subsequent satisfactory healing of the stump. In the entire series there is not an instance of leakage from the bronchial stump when a serious effort had been made satisfactorily to close it. In one of the two instances in which leakage occurred, the simplest possible procedure was purposely used, the bronchus being simply ligated with a single fine silk (No. A) ligature. In the other instance a metal band was intentionally flattened instead of being rolled, and the probable necrosis of the bronchial wall at the proximal edge of the band was predicted. In dogs, then, it may be said that the satisfactory closure of the bronchial stump is possible. Infection, which played so large a rôle in the mortality in earlier experimental work,[4] has been eliminated as a factor in experimental lung

[2] In every case which came to autopsy the tight closure of the bronchial stump was determined by immersing the stump in water and forcing air under high pressure into the trachea. The failure of air to escape from the bronchial stump was taken as an evidence of a satisfactory closure.

[3] In this part of the work, Heuer and Holman were associated and will subsequently publish in more detail the results of this phase of the work.

[4] Schmid, Hans: Experimentelle Studien über partielle Lungenresektion. Berl. klin. Wchnschr., 1881, XVIII, 757-759.

Lost 5 out of 8 dogs operated upon: 4 from sepsis, 1 from presumed acute carbolic acid poisoning. He resected the apex of the lung only. His technic evidently was inadequate. His instruments and ligatures were apparently not boiled; simply placed in salicylic acid.

Gluck, T.: Experimenteller Beitrag zur Frage der Lungenextirpation. Berl. klin. Wchnschr., 1881, XVIII, 645-648.

Extirpated the lung in 6 dogs and 14 rabbits. A "few" of the rabbits developed pericarditis and septic pleurisy between the seventh and tenth days after operation. The operations were done under antiseptic precautions.

Block: Experimentelles zur Lungenresection. Deutsche med. Wchnschr., 1881, VII, 634.

Before undertaking the experiments the author studied the methods of Lister at the clinics of Küster and Volkmann. His first series of experiments consisted of the extirpation of the lung in 5 rabbits and 4 dogs. In no instance was he able to keep the animals alive longer than 14 days. The rabbits died for the most part immediately after operation; the dogs lived to the fourteenth day. Sepsis was the cause of death in the animals which did not die immediately. A month later he undertook a second series of experiments. All of the four animals submitted to operation died of a fibrinous hemorrhagic pleuritis.

Biondi, D.: Lungenextirpation bei experimentell lokalisirter Tuberculose. Med. Jahrbücher, 1884, 207-216.

His experiments are complicated by the initial injection of tubercle bacilli into the lung, in the attempt to produce a localized pulmonary tuberculosis. About 25 or 35 days after the initial injection of tubercle bacilli the animals were operated upon and the lung resected. He made use of 10 rabbits, 6 cats and 5 dogs. About half the total number died of septic pleuritis or pericarditis after the initial injection. Four animals died immediately after the extirpation of the lung. Only 7 animals survived the extirpa-

excision. In the above series, with the exception of one of the cases cited above, in which leakage of the bronchial stump was followed by a pleural infection, there was no instance of infection of the parietal wall or pleura. That the infections in previous experimental work were due to faulty technic in the conduct of the operation exclusive of the treatment of the divided bronchus would seem evident from our earlier experiments, in which, after division of the main bronchus, a culture was made from the bronchial mucous membrane near the bifurcation of the trachea. These cultures were almost invariably sterile, a finding which in the absence of leakage from the stump would largely eliminate the bronchial mucous membrane as a factor in the causation of pleural infections. That the pleura is peculiarly susceptible to infection, as has been quite generally believed—and largely as result of the incidence of infection following experimental intrathoracic operations—would not seem to be borne out by some experiments that are not yet completed. The occurrence of pleural effusions following lung excision as a factor in the mortality—commented upon by a number of authors—will be discussed when we come to discuss the reaction of the pleura following pneumectomy. It may be stated here that our experiments would indicate that the occurrence of pleural effusions after excision of the lung is probably entirely the result of infection of the pleura and rightfully should play no rôle in the mortality. In the absence of complicating factors (distemper, etc.), and with an adequate technic and careful closure of the bronchial stump, the mortality in experimental pneumectomy in dogs—previously very high—may be reduced to a minimum.

Pathological-physiology of the Circulation and Respiration During and After Total Lung Excision.—In the course of every operation, the heart's action was carefully noted; and one reason for performing pneumectomy upon the left side was that the heart was directly under the operator's vision during the procedure. In only one animal of the entire series was there a spontaneous cardiac upset during operation. In this, a very old dog, a marked dilatation of both auricles and of the right ventricle was noted immediately on opening the chest. The heart's action was very slow, and it was questionable in our minds whether we ought to proceed with the experiment. Just at the completion of the pneumectomy the heart stopped beating. After direct massage of the heart the cardiac beat returned and the operation was completed. The animal recovered and was sacrificed eight months after operation. At our repeated examinations of this dog after operation, no cardiac irregularity nor dyspnea were noted. With this exception there were apparently no effects upon the heart's action from ligation of the pulmonary arteries and veins of one lung, nor from division of the main bronchus or its branches. There was no change in the cardiac movements after the lung had been removed. These statements hold true if the procedures are carried out with gentleness. It was noted in our earlier experiments that too strong traction upon the lung or bronchus, intentionally exerted, caused most commonly a slowing of the heart, followed sometimes by marked irregularity in its beat. In practically every animal in which the experiment was tried cardiac disturbances could be produced by traction upon the bronchus. The degree of inflation of the lungs also was found to have a marked effect upon the heart's action. In the dog, too little inflation most commonly caused a slowing of the heart beat, and, with the slowing of the heart there occurred very often a dilatation of the auricles. The effect upon the pulse and blood pressure of the various procedures necessary in carrying out lung excision may be seen in the accompanying tracing (Fig. 1). An examination of this tracing will show that ligation of the pulmonary arteries and veins, division of the bronchus, and removal of the entire lung, have little or no effect in dogs upon the pulse or blood pressure.

The effect of the procedure upon the respiration could not be determined during operation. So far as possible the normal respiratory rate and the normal inflation of the lung, not the object of our attack, were maintained during the experiment by the intratracheal anesthesia apparatus. At the moment the chest was completely closed by the approximation of the adjacent ribs, the remaining lung was moderately distended. The intratracheal tube was then removed and the closure of the wound completed without artificial inflation of the lung. It was commonly noted that moderate dyspnea appeared after removal of the intratracheal tube and continued for several hours. In only one animal was marked dyspnea noted. By the morning following the operation (performed in the afternoon) the dyspnea had in the majority of cases disappeared,

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tion of the lung. Although the author states that he used great care in his technic, 9 animals developed a septic pleuritis following the extirpation of the lung.

Murphy, J. B.: Surgery of the lung, J. Am. M. Ass., 1898, XXXI, 151, 208, 281, 341. Five of the nine animals operated upon died of sepsis.

Robinson, Samuel: Ann. Surg., 1908, XLVII, 184.

In 30 thoracotomies upon dogs performed under positive pressure anesthesia (of which 12 were simple pleurotomies without interference with the lung, 15 with resection of a part of or an entire lobe, 1 with removal of two entire lobes, and 1 with removal of the entire lung) there were 5 deaths from sepsis, one case of sepsis being due to leakage from the bronchial stump, and four additional cases of infection (either localized empyema or parietal wound infection) the animals, however, recovering.

Halsted, W. S.: Tr. Am. Surg. Ass., 1909, XXVII, 111.

In 21 consecutive thoracotomies there was only one primary infection of the thorax—a marked contrast to the hitherto reported results.

Meyer, Willy: Zentralbl. f. Chir., 1909, XXXVI, 1713-1716. *Also:* J. Am M. Ass., 1909, LIII, 1978.

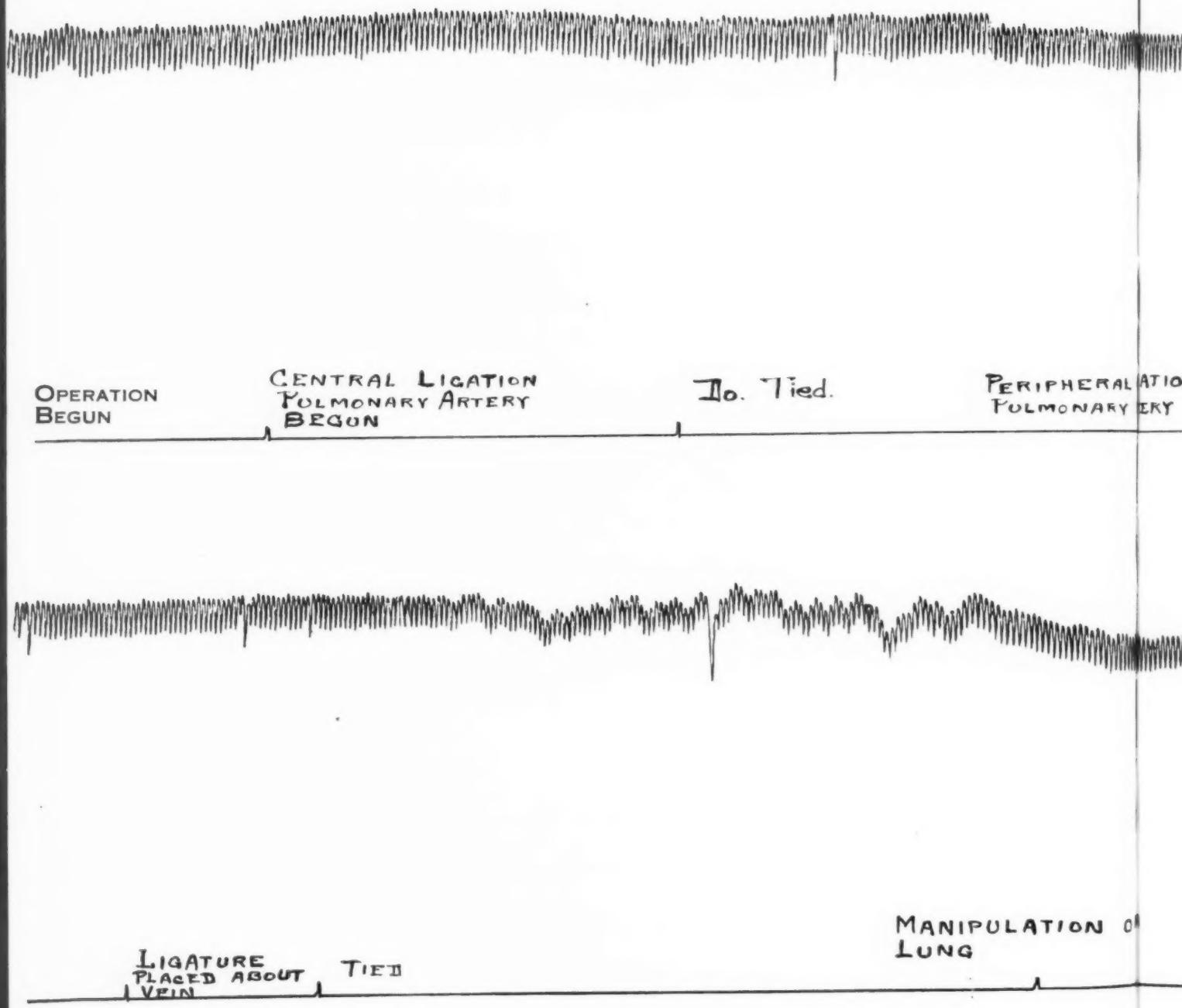
In 21 total extirpations there was one death due to sepsis and one due to leakage from the bronchial stump.

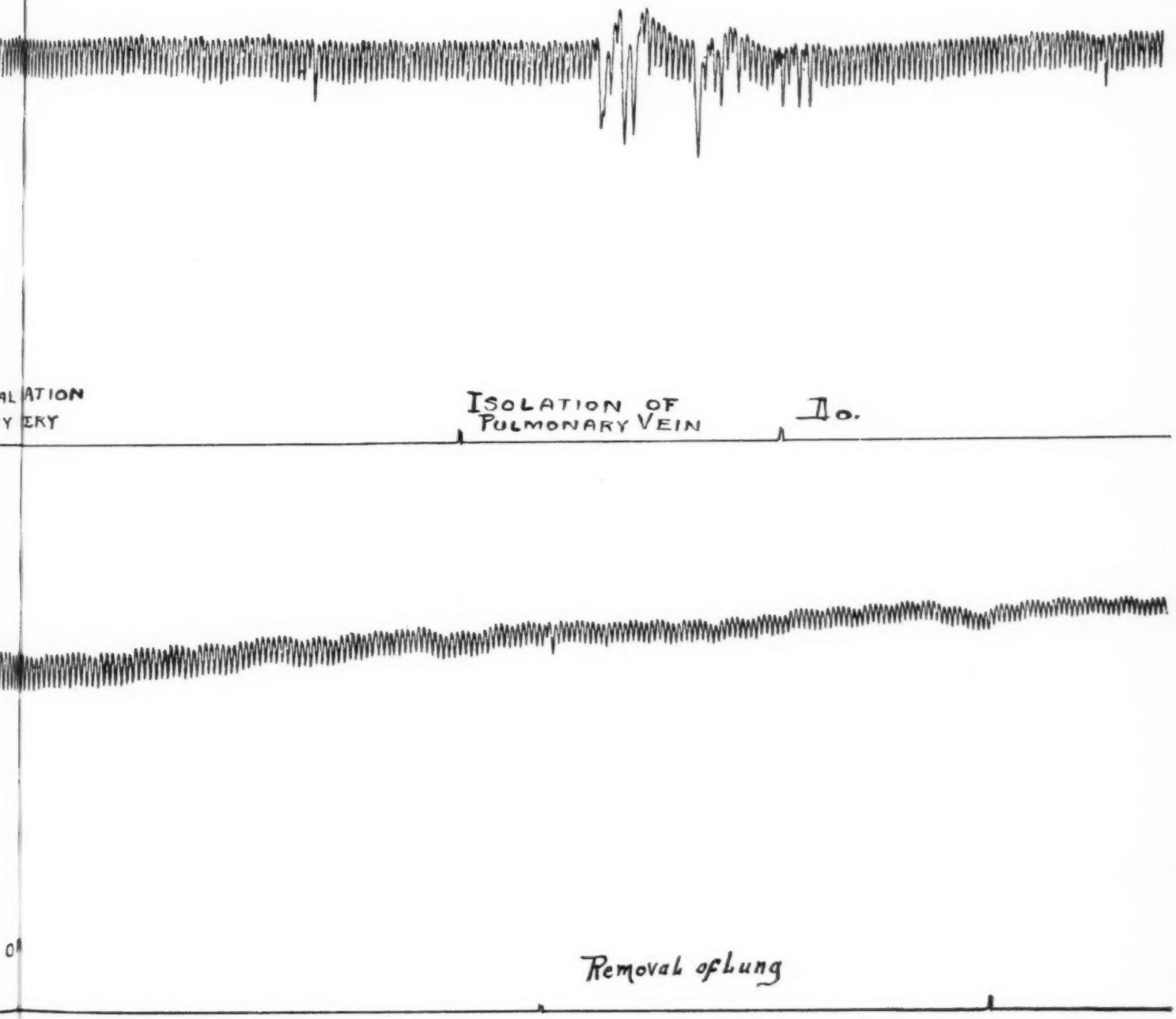
Robinson and Sauerbruch: Deutsche Ztschr. f. Chir., 1909, CII, 542-560. *Also:* Zentralbl. f. Chir., 1910, XXXVII, 391.

In 38 simple total extirpations of the lung under positive pressure (including those of Haecker) there were only four recoveries. In 18 there occurred a marked transudation into the pleural cavity upon the operated side (infection?) followed by death; five animals died from sepsis, 11 from leakage from the bronchial stump.

Kawamura, K.: Deutsche Ztschr. f. Chir., 1914, CXXXI, 189-222.

Of 23 animals operated upon, 3 died of sepsis, 2 cases being secondary to leakage from the bronchial stump.


OPERATION BEGUN
CENTRAL LIGATION PULMONARY ARTERY BEGUN
No. Tied.
PERIPHERAL PULMONARY
LIGATURE PLACED ABOUT VEIN
TIED
MANIPULATION OF LUNG


ISOLATION OF PULMONARY VEIN
Ao.
Removal of Lung

and in the subsequent course dyspnea was never conspicuously present. The animals, kept under observation for from several months to a year, were as active as other animals, and after running about the yard showed no more dyspnea than did normal animals.

Treatment of the Bronchial Stump.—Although the treatment of the bronchial stump is the essential and still unsolved problem in lung excision in man, we were rather diverted from this phase of the subject and did not try a number of methods of closure which have been suggested and used by others. The procedure suggested by Henschen[5] of introducing a roll or plug of fascia into the lumen of the divided bronchus and closing the stump over it—quite independently thought of and successfully carried out in dogs by Dr. Halsted and later by Crowe—was not tried; nor were the various methods of fascial transplants, as suggested by Henschen and others. We did not, moreover, test the possibilities of fascial or metal bands, although a very successful result as regards occlusion and healing was obtained by the latter method. The procedures which were carried out may be grouped as follows:

1. Crushing of the isolated bronchus; closure of the divided bronchus by a single ligature of heavy (No. EE) or medium (No. C) silk, which transfixes the bronchial wall. The crushing of the bronchus with a clamp was depended upon to crush the bronchial mucous membrane. In our earlier experiments the stump after ligation and section was treated with pure carbolic acid. After cultures from the mucous membrane quite uniformly showed no organisms, this step was omitted. The bronchial stump was dropped back into the pleural cavity and purposely not covered with a fold of pleura or pericardium, in order to eliminate a covering of this sort as a factor in the healing. This method was carried out in eight animals (L^1, L^2, L^3, L^6, L^8, Y^1, Y^6, Y^{12}).

Results.—In none of the eight animals in which this simple procedure was carried out was there any leakage from the bronchial stump or pleural infection. Three of the animals are at present living and healthy about seven months after operation. Four animals died of distemper—1 one month, and 3 three weeks after operation. One animal was sacrificed eight months after operation.

Healing of the Bronchial Stump.—Although we intentionally did not cover the bronchial stump with a fold of pleura or pericardium, autopsy in the five animals which died or were sacrificed showed in all that the bronchial stump had retracted into the mediastinal tissues and was covered with a glistening membrane which could not be differentiated from the mediastinal pleura. The covering of the stump was often so perfect that not even a scar of any sort indicated its location, and only by traction upon the trachea could its position be determined by the dimpling of the pleura. In some of the specimens the position of the stump could be recognized by the silk ligatures which were visible through the glistening overlying membrane. In only one animal of this group was there a scar upon the mediastinal pleura sufficiently large to show in a photograph (Fig. 2, *a*). When the bronchial stump is dissected out carefully, its end is found either smoothly rounded or more commonly bulbous, as if capped by a mass of fibrous tisue (Fig. 3, *A* and *B*). A mesial section of the bronchial stump invariably shows a solid obliteration of the end of the stump by scar tissue (Figs. 4, 5, and 6). The black silk ligatures can be seen embedded in the scar. The bronchial mucous membrane everywhere lines the lumen of the stump. Microscopic sections of the occluded ends of the stumps, shown in Figs. 4, 5 and 6—which may be taken as types—show the following:

L^2 (Mesial gross section, Fig. 4. Microphotograph, Fig. 7). The occluded end of the bronchus consists of a mass of fibrous tissue in which are scattered numerous fragments of cartilage. Here and there are blood vessels seen in cross-section, and almost in the center of the mass is a cleft (a) completely lined with bronchial mucosa and evidently either a prolongation of the lumen of the bronchus or an isolated space closed off from the main lumen. A fold of the bronchial wall (*b*) projects into the bronchial lumen and consists largely of masses of cartilage. The internal surface of the mass is everywhere covered with mucous membrane, excepting at one point where a ligature of black silk (*c*) is in the process of being discharged into the bronchial lumen. There is a marked reaction about the silk ligatures. They are surrounded by a zone of small round cells in which foreign-body giant cells are fairly numerous.

L^3 (Mesial gross section, Fig. 5. Microphotograph, Fig. 8). A very similar picture to L^2 above. Again, in the mass of fibrous tissue which occludes the end of the bronchus is a space (*a*) completely lined with mucous membrane and partly filled with cells with small round nuclei.

L^6 (Mesial gross section, Fig. 6. Microphotograph, Fig. 9). Again, a very similar picture to L^2 and L^3 above. There are fewer cartilage masses, and the fibrous tissue covering the stump is less cellular. There is a greater reaction about the silk ligatures. Seen in cross-section, each is surrounded by a wide zone of small round cells in which are very numerous foreign-body giant cells.

2. A modification of the above procedure. The attempt was made to secure a longer bronchial stump. After division of the pulmonary arteries and veins the lung tissue was stripped by gauze dissection, not only from the main bronchus but from the primary branches of the main bronchus. The two primary divisions of the main bronchus were individually crushed, ligated with a transfixion suture, and divided. When allowed to drop back, the long naked branching bronchial stump projected into the pleural cavity a distance of 3 or 4 cm. No attempt was made to cover it with pleura or pericardium. The reason for this procedure was twofold: (a) In man, it has been constantly stated that the bronchial stump is so short that any method of treatment aside from a simple mass ligature is not feasible. If that be the case, could not the lung be stripped from the main branches of the primary bronchus and these treated by the methods employed for the main

[5] Henschen: Experimente zur intrathorakalen Lungenchirurgie. Beitr. z. klin. Chir., 1914, XC, 373.

bronchus? (b) It was early noted that these two factors influenced the ease and therefore the safety of bronchial occlusion by the commonly employed methods—the size of the bronchi and the rigidity of the cartilages. In large old dogs the closure of the bronchial stump is a more difficult procedure than in small young animals. In the same animal the smaller the lumen and the less the rigidity of the bronchi, the easier is the occlusion; conditions which are more likely to obtain in the primary divisions of the main bronchus.

Results.—In two dogs (L^1 N. S., L^2 N. S.) this method was employed. In one the usual care in the closure of the bronchi was exercised and heavy black silk (No. EE) was used for the ligatures. This animal recovered and was sacrificed eight and a half months after the operation. In the other, intentionally and perhaps foolishly, the bronchi were not crushed but were simply ligated with a transfixion ligature of fine silk (No. A). For a week after the operation this animal appeared perfectly well and then was found dead in his cage. Autopsy showed the wound perfectly healed; the pleura was everywhere smooth, glistening, and not injected; there was not a drop of fluid in the empty pleural cavity. On immersion of the bronchial stump in water, air forced into the trachea bubbled through a tiny point in the wall of the upper of the two bronchi. Dissection of the stump showed that the fine silk ligature had cut through the bronchial wall at one point. Death therefore was due to an acute pneumothorax from leakage from the bronchial stump.

Healing of the Bronchial Stump.—Although the bronchial stumps in these two animals were unusually long and projected a considerable distance into the pleural cavity, as in the above series, they had retracted and were covered by the mediastinal pleura. In the animal which died and was autopsied one week after operation, the covering of the bronchi was not quite complete. The lower of the two bronchi was completely covered by a smooth glistening membrane; the upper, however, was uncovered at its tip over an area 4 mm. in diameter. It was through this uncovered area that air escaped into the pleural cavity. An examination of Figs. 10, 11 and 12 will show the nature of the healing of the bronchial stump. Although we might expect that by this method the healing would be identical with that in Method 1, an examination of the only specimen that we have shows distinctly less scar tissue formation. The stumps of the two bronchi are nicely rounded (Fig. 10) and do not show the hard mass of scar tissue at the end of the stump noted in the previous series. A mesial section of the specimen (Fig. 11) shows the two primary divisions of the main bronchus separated by a ridge of tissue composed largely of cartilage. The end of each primary division is rounded, nicely healed, and without the mass of scar tissue seen in the examples described under Method 1. These rounded ends are made up of fibrous tissue, in thickness approximating the walls of the bronchi, covered without (externally) by the mediastinal pleura, within by the bronchial mucous membrane. On gross examination, no cartilage is present in this wall of scar tissue, and one has the impression that the walls of the bronchi previously apposed by the ligature have in part separated, the intervening space being filled with scar tissue. In the primary subdivision to the left in the illustration a silk ligature lies free in the lumen. Microscopic section (Fig. 12) shows the septum (*a*) between the two subdivisions of the main bronchus provided with normal cartilage. The ends of the two subdivisions of the main bronchus have been occluded almost entirely by scar tissue. In the bronchus to the right in the illustration, no cartilage is demonstrable; in that to the left, one or two small fragments of cartilage may be seen. The bronchial mucous membrane lines the inner wall of fibrous tissue. In the healing of the bronchial stump in this case, therefore, the bronchial wall seems to have played but little part. One has the impression that the walls of the bronchus approximated by ligation, have separated, the defect being filled with scar tissue.

3. A modification of Method 2. The arteries and veins were ligated and divided, as in the preceding methods. The lung tissue was stripped from the two primary subdivisions of the main bronchus. The two secondary bronchi were individually crushed and ligated as in Method 2. The main bronchus and the two secondary bronchi were then crushed so as to destroy the mucous membrane, and the main bronchus inverted or folded upon itself longitudinally. This procedure brought the two secondary bronchi into apposition. The apposed walls of the main bronchus were fastened together by a series of interrupted fine silk sutures; the apposed secondary bronchi were sutured together with mattress sutures.

Results.—Only one animal (L^9 N. S.) was treated by this method. The procedure was carried out on a large dog and was quite feasible. The animal died two and a quarter months after operation. At autopsy the wound was entirely healed and the scar quite invisible. The left pleural cavity was without a drop of fluid and the pleura showed no evidence of infection. The right lung was voluminous, crepitant, and on section showed no evidence of pneumonia. The abdominal viscera were normal. The animal showed a remarkable degree of emaciation, and the only explanation of his death was starvation.

Healing.—The bronchial stump had retracted and was covered by a smooth glistening membrane. Gross examination of the stump shows the end bulbous (Fig. 13) and, on palpation, hard and solid as if composed of fibrous tissue. The identity of the two subdivisions of the main bronchus, apposed and sutured together at the time of the operation, is quite lost. Mesial section through the stump shows an interesting picture (Fig. 14). The lumen of the main bronchus is filled by a mass which is composed largely of cartilage mixed with fibrous tissue and which represents the remains of the longitudinally inverted bronchial wall and the apposed secondary bronchi. Between the mass and the bronchial wall is a cleft lined on either side with normal bronchial mucous membrane. In other words, the inverted portion of the bronchial wall has not become adherent to the uninverted portion (probably due to insufficient crushing of the mucous membrane), and although it fills the lumen of the bronchus it does not obliterate it. The end of the bronchial stump is composed of a dense mass of

tissue in which cartilage and scar tissue are inextricably mixed and in which the identity of the two subdivisions of the main bronchus is completely lost. In this mass may be seen the silk sutures used in the closure. Microscopic section (Fig. 15) shows the end of the bronchus obliterated by a mass of tissue composed of fibrous tissue and cartilage fragments. The infolded portion of the bronchial walls is viable and fills the lower end of the bronchus but does not completely obliterate it. The clefts between the infolded and normal bronchial walls may be seen at *a* in the illustration. These clefts are lined with normal mucous membrane. Here and there in the section (as at *b*) the mucosa of the normal bronchial wall has fused with that of the infolded portion. Our conception of this method is that the infolded wall of the bronchus may quite satisfactorily occlude the bronchial lumen, but presumably will not completely obliterate it unless the bronchial mucous membrane is adequately crushed or removed.

4. The usual ligation and division of the pulmonary arteries and veins. The isolated main bronchus was bisected, the mucous membrane removed, and the two halves of the bronchus flattened together and held with a series of sutures around the edges, together with interrupted through and through sutures which encircled the cartilages. This method was described by Dr. Halsted [6] and his success with it led us to dismiss it after one experiment.

Results.—The method was used in one animal (L^4). He recovered from the operation but died three months later from distemper. Autopsy showed the external wound perfectly healed. The pleura was glistening and not injected. There was no fluid in the left pleural cavity. The stump had retracted, was covered with a glistening membrane and was quite invisible. Tested for in the usual way, there was no leakage. The right lung showed an extensive bronchopneumonia. There was a small amount of free cloudy fluid in the right pleural cavity.

Healing.—The retraction and covering of the stump by the mediastinal pleura had occurred as in the previously described methods. On dissection of the stump it was found capped by a mass of scar tissue (Fig. 16). A medial section of the stump (Fig. 17) shows its total occlusion by a mass of scar tissue, in the center of which may be seen the cartilages of the apposed bronchial walls. The scar tissue is therefore extrabronchial and not intrabronchial. The silk sutures are seen in this scar tissue outside the apposed bronchial walls. Microscopic section (Fig. 18) shows the occluded end of the stump composed of fibrous tissue, in the center of which are seen in section the cartilages apposed at the time of operation. As compared with sections by Method 1, the scar tissue lies in general external to the cartilages rather than being intermixed with cartilage masses. The mucosa lines the lumen of the bronchus completely, excepting at one point where again a ligature apparently is in process of being discharged into the bronchial lumen.

[6] Halsted, W. S.: Clinical and experimental contribution to the surgery of the thorax. Trans. Am. Surg. Ass., 1909, XXVII, 119.

5. Isolation of the main bronchus; crushing; ligation with a transfixing ligature of medium or heavy silk. Carbolization of the stump. Inversion of the stump under a purse-string suture or several sutures. The method is that of Willy Meyer [7] and is identical with the common method of treating the appendix stump.

Results.—The bronchial stumps in nine animals were treated by this method (L^5, L^7, L^9, L^{10}, L^{11}, L^{12}, L^{13}, L^{14}, and Y^{11}). The method was tested thoroughly on animals of various sizes because of the criticism by a number of authors that it only occasionally is feasible. In all the animals the method was perfectly feasible, although it became more difficult the larger the lumen of the bronchus and the greater the rigidity of its walls. One of the dogs is at present living and healthy, seven months after operation; two animals sent to the farm for the summer were lost, one of which was known to be living ten months after operation, the other, three months after operation. One animal died three weeks after operation. At autopsy there was no infection of the parietal wound or pleura, nor leakage from the bronchial stump. Death was due to pneumonia of the remaining lung. The remaining five animals were sacrificed at varying intervals up to one year after operation.

Healing.—Dissection of the bronchial stumps showed in some a bulbous end (Fig. 19), in others a tapering or rounded end (Fig. 20). Mesial sections of the bronchial stumps show in all a very satisfactory occlusion of the stump. The interesting features observed in the healing by this method may be seen in Figs. 21 to 25, showing five of the specimens. The first (Fig. 21) is a beautiful example of a perfectly inverted stump. The walls of the inverted portion of the bronchus, apposed by the ligature, have remained in contact with each other and have solidly united. The bronchial mucous membrane covers the inverted portion of the bronchus. The purse-string sutures may be seen embedded in the scar tissue which caps the bronchial stump. In the second, Fig. 22 (animal sacrificed one year after operation), the healing is similar, but with the difference that the inverted portion of the bronchial wall has become flattened down and greatly thinned as compared with that in the preceding specimen. The specimen is interpreted as a later stage of healing by this method than in the preceding specimen. An examination of the third (Fig. 23) (from an animal dying three weeks after operation from pneumonia) shows that the walls of the inverted portion of the bronchus (*a*) previously apposed by the ligature, have separated, the space between them forming a cavity (*b*), which communicates with the lumen of the trachea and which is lined with granulation tissue and partly filled with a mass of silk. A fairly broad and solid mass of scar tissue separates the cavity from the exterior, and although the healing is incomplete and imperfect, it is quite effective. In the fourth (Fig. 24) (from an animal dying two weeks after operation from distemper) similar conditions obtain; but here the cavity formed by the separation of the previously apposed inverted bronchial walls (*a*)

[7] Meyer, Willy: Pneumectomy with the aid of differential air pressure; an experimental study. J. Am. M. Ass., 1909, LIII, 1978.

has become partially, though not completely, filled with scar tissue. In the fifth (Fig. 25) (from an animal sacrificed seven months after operation) what appears to have been a space between the separated inverted bronchial walls has become filled with a solid mass of scar tissue which quite occludes the entire short bronchial stump. A narrow cleft (*a*) lined with mucous membrane separates the inverted from the noninverted portions of the bronchial wall. In this group of cases healing took place either perfectly, as shown in the first or second specimen, or imperfectly, the succeeding stages of which are shown in the third, fourth, and fifth specimens. Microscopic sections confirm our interpretation of the gross specimens, with one exception. In the section (Fig. 26) of the specimen shown in Fig. 21, the occluded end of the stump consists of a mass of scar tissue which lies completely below the cartilages of the inverted stump. The cartilages of the bronchus can be readily followed into the inverted portion of the stump. There is no intermingling of cartilage and fibrous tissue, as seen in Method 1. The scar tissue caps the inverted portion of the stump and fills the space between the inverted walls. The mucosa completely lines the inverted stump. In the section (Fig. 27) of the specimen shown in Fig. 22, the inverted portion of the bronchial stump has become flattened down. The cartilage masses are very much less in evidence. The occluded end of the bronchus is made up largely of dense fibrous tissue. In the section (Fig. 28) of the specimen shown in Fig. 23, the walls of the inverted portion of the stump have been separated widely so that the inverted portion of the bronchial wall (as seen in section) is almost in contact with the uninverted portion on either side. There is, therefore, a wide space or cavity between the inverted walls of the bronchus which communicates with the lumen of the bronchus. This cavity is filled with a mass of silk and blood clot (*a*). Evidently the silk is about to be discharged into the bronchus. Below this cavity and separating it from the exterior is a broad firm mass of scar tissue. The cavity is lined, not with mucosa but with granulation tissue. What has apparently happened in this case is that the ligature about the inverted stump has slipped off or cut through, allowing the inverted walls of the bronchus to spring apart. The closure of the stump, however, from the standpoint of adequacy is satisfactory. In the section (Fig. 29) of the specimen shown in Fig. 24, the walls of the inverted portion of the bronchus are again seen to have sprung apart. What was evidently a space or cavity between the separated bronchial walls has become partly filled with newly formed granulation or scar tissue which is abundantly vascularized. The mucosa almost completely covers this newly formed tissue. The same process has therefore apparently occurred in this specimen as in the above, but may be interpreted as a later stage in the healing. In the section (Fig. 30) of the specimen shown in Fig. 25, we find that our interpretation of the gross specimen in this case would seem an error. The central portion of the inverted stump consists of a mass of cartilage fragments, external to which is a layer of loose fibrous tissue covered completely by mucous membrane. The ligature (*A*) lies external to the cartilages of the inverted stump and evidently has not cut through. The walls of the inverted stump therefore have not separated and the healing is as perfect as in the first two specimens described above.

6. After crushing and ligating the bronchus, a metal band, such as has been used by Dr. Halsted in his arterial work, was placed around the bronchus and tightly rolled. In a second instance, a metal band after being rolled, was flattened with a crushing clamp, and, although the impropriety of the procedure was recognized as soon as it had been done, the band, nevertheless, was left in place.

Results.—The procedure was carried out in two animals (L^{8} N. S. and L^{10} N. S.); in one the band was tightly rolled, in the other it was flattened with a crushing clamp. The animal in whose case the band was rolled recovered and was sacrificed six months after operation. The animal in whose case the band was flattened died four days[8] after operation. At autopsy the pleural cavity contained a considerable amount of bloody purulent fluid. The bronchial stump showed a necrosis of its wall at the upper (proximal) edge of the band with a perforation 3 mm. in diameter.

Healing.—In the animal which died four days after operation the end of the stump was found uncovered by the mediastinal pleura. The metal band was partly visible but was largely covered with exudate. At the upper margin of the band there was an evident necrosis of the bronchial wall with an opening into the bronchial lumen 3 mm. in diameter (Fig. 31, *b*). On attempts to remove the metal band (Fig. 31, *a*) it was found encrusted with what appeared to be a crystalline material (specimen preserved in formalin) and had become brittle so that it broke when we tried to remove it. On removal of the metal band the tissue beneath it was of extraordinary hardness, and evidently the bronchial wall beneath the band had been converted into a solid cord. On section (Fig. 32) the tissues beneath the band (*a*) consist of a solid mass made up largely of cartilage in which the silk ligature is seen. The necrosis of the bronchial wall has occurred at the upper border of the solid cord (*b*). Microscopic section of the solid cord of tissue beneath the band (Fig. 33) shows that it is made up almost entirely of masses of cartilage, in the spaces between which is a varying amount of fibrous tissue. There is no evidence that the band has cut through the bronchial wall; and it is evident that the solid cord of tissue is the closely compressed and folded bronchial wall. The cartilage masses are clearly defined but the nuclei in the majority of the cartilage masses fail to stain. This is especially true of the marginal cartilages (those immediately under the band). In a single large centrally placed cartilage the nuclei are well stained. The impression one gathers from an examination of the specimen is that the cartilages underneath the band have died.

In the animal which was sacrificed six months after operation the stump had retracted and was covered by the glistening mediastinal pleura. On removal from the body, the stump

[8] Possibly the dates in our notes of this case are incorrect. It seems to us unlikely that such marked changes in the structures under the metal band could have taken place in so short a time.

was rounded and extremely hard on palpation (Fig. 34). On section (Fig. 35) the bronchus beneath the band (*a*) has been converted into a solid cord. External to the band and covering it completely is a wall of fibrous tissue 1.5 to 2 mm. in thickness; beneath it is a solid mass of tissue which completely occludes the bronchus. On gross examination of the external covering of the band no cartilage can be identified and the impression given is that the band has not cut through the bronchial wall. In the mass of tissue beneath the band cartilage cannot be positively demonstrated. Microscopic section (Fig. 36) shows the cartilage of the bronchial wall above the band turned in and approximated but not completely. The space (*aa*) is that previously occupied by the metal band. The tissue external to this band (*C*) is newly formed fibrous tissue which completely covered the band. In this layer of fibrous tissue there are no cartilage masses or other structures to indicate that the metal band has cut through the bronchial wall. Within the space (*aa*) is the solid cord of tissue (*b*) beneath the metal band. This is made up of a dense tissue with closely packed nuclei, some polymorphous, others large and granular. There are many foreign-body giant cells. Nowhere can any cartilage masses be recognized, and presumably they have undergone death and disappeared. The impression given by the examination of this section is that the metal band has not cut through the bronchial wall, that the solid cord of tissue represents the bronchial wall, but that the structures composing it have entirely disappeared and have been replaced by a conglomerate mass of fibrous tissue.

It would be of little profit to discuss at length the various methods of treating the bronchial stump used in experimental lobectomy and pneumectomy. Briefly stated, these methods may be grouped as follows:

1. A simple mass ligature in the neighborhood of the hilus (Lenhartz, Robinson, Sauerbruch); used by us in eight animals.

2. The covering of the closed bronchus with a small fragment of lung tissue (Garrè).

3. Proximal ligature of the bronchus. Incision through lung tissue near the hilus. Second ligation of bronchi presenting on the cut surface of the lung. Closure of the lung over the ligated bronchi (Tiegel).

4. A procedure similar to (3) above, but without the proximal ligature (Kawamura).

5. A transfixion ligature to close the bronchus. A second ligature (of catgut) central to this which is tied loosely (Friedrich).

6. A procedure similar to (5) above, but with a double tight ligature of silk and with covering of the stump by a fold of pericardium (Schlesinger).

7. Inversion under sutures of the ligated bronchial stump, as in the appendix operation (Willy Meyer).

8. Bisection of the bronchus. Removal of the mucous membrane. Apposition and suture of the bisected bronchial walls (Halsted).

9. Crushing of the bronchus. Closure of the bronchus with mattress sutures. Covering of the stump with a transplant of fascia lata. Covering of the stump so treated with a fold of pleura or pericardium (Giertz).

10. Division of the bronchus. Removal or not of the mucous membrane. Insertion into the lumen of a plug of fascia lata. Closure of the bronchus by ligature (Henchen, Halsted, Crowe).

The multiplicity of methods is an index first, of the inadequacy in the hands of investigators of the methods used by their predecessors; and second, of the attempt to find a method which can safely be used in man. Although no one method was given a very extensive trial, our experiments would indicate that in dogs every method indicated above—and others which we employed—are technically feasible and if carefully done even the simplest (simple transfixion ligature of the bronchus) is adequate to ensure a satisfactory closure of the bronchial stump. From a study of the gross and microscopic sections of the bronchial stumps in our series it would be difficult to state which method is followed by the most satisfactory occlusion and healing. From experimental findings alone, therefore, it is difficult to say which method may most safely be employed in man. When we review the literature of lobectomy (not resection) in man we find that a simple mass ligature has been almost universally employed, the various other methods used in experimental work being impracticable because of the shortness of the bronchial stump. That this method has been inadequate is abundantly indicated by the frequency of leakage of the bronchial stump, and by the high percentage of postoperative bronchial fistulæ.

Reaction of the Pleura Upon the Operated Side.—A common result of experimental total pneumectomy by previous observers has been the development of a clear or slightly turbid serous or serosanguineous effusion into the pleural cavity. It has been stated to occur quite independently of infection and to be responsible for a certain mortality. A pleural effusion in the dog, if small, may readily escape detection by physical examination, but even the small effusions (less than one ounce) may be recognized by fluoroscopic examination after the lung has been removed. Owing to the lack of an X-ray apparatus in the laboratory and often the impossibility of arranging examinations at the busy X-ray department of the hospital, not every dog was followed fluoroscopically. But so far as was possible, fluoroscopic examinations were made the day following operation and on succeeding days, and we wish to thank Miss Smith and Miss Black, of the hospital X-ray department, for their assistance in this part of the work. Moreover, at the autopsies of the animals which died or were sacrificed days, weeks, or months after operation, the presence of even a drop of the fluid in the pleural cavity from which the lung had been removed was invariably carefully noted. Our observations have been quite constant. Neither in the days immediately following operation nor in the course of weeks or months after operation does, so far as we have been able to determine, any fluid, even the smallest amount, accumulate

in the pleural cavity.[9] When, on the other hand, infection occurs, there follows invariably a pleural effusion.[10] We are inclined to believe, therefore, that the pleural effusions which have occurred in the experience of others have been the result of pleural infections.

The Fate of the Pleural Cavity on the Side of Operation and the Method of its Obliteration.—Within two, three, or four days after operation, fluoroscopic examination shows that the heart has definitely moved over toward the empty pleural cavity. Usually within two weeks the heart is in contact with the chest wall, and by fluoroscopic examination the pleural cavity appears to be obliterated except for a cleft between the base of the heart and the apical region and a space between the apex and lower border of the heart and the costodiaphragmatic angle. In the succeeding weeks these two clefts become narrower, but, as determined by fluoroscopy, they may persist for long intervals. A recent examination of four dogs still under observation seven months after operation shows apparently these two clefts still present; in other words, that the obliteration of the pleural cavity is not yet complete (Fig. 37). We must not, however, attempt to draw too positive conclusions from fluoroscopic examinations, for the lung of the dog is so little resistant to the penetration of the X-rays that we may be mistaken in our interpretation; indeed, we think it probable that in Fig. 37, for example, the triangular space to the left of the cardiac apex is occupied by lung tissue. Examination of animals dying or sacrificed weeks or months after operation and fixed in formalin as previously described, confirms, however, in general our fluoroscopic findings. The heart first comes into contact with the chest wall, a superior and inferior space above and below the heart persists for variable time,—and may persist for months (seven or eight),—but eventually disappears (Figs. 38, *a;* 39, *a;* and 40). Obliteration of the pleural cavity from which the lung has been removed begins, then, practically immediately after removal of the lung, is largely accomplished within two or three weeks, may be complete in six to eight weeks, but may not be entirely complete for six months or more.

There are three factors which contribute toward the obliteration of the cavity: the dislocation of the heart and remaining lung toward the side operated upon, the flattening or contraction of the thoracic wall with its attendant scoliosis, and the elevation of the diaphragm. Of these the heart and lung play by far the largest rôle. In early stages of the obliteration of the cavity the heart is in contact with the chest wall and the lung has extended far beyond the midline before either of the other two factors come into play. The heart has apparently only a passive part in this process, being simply pushed over toward the affected side by the enlarging lung. While we have noticed in animals sacrificed six to eight months after operation what appears to be an enlargement of the heart, we have not sufficient evidence to say, as has been stated by one observer, that the heart undergoes hypertrophy following excision of the lung.[11] In the late stages of obliteration of the cavity, the superior and inferior spaces become obliterated largely by the lung. In left-sided pneumectomies, for example, the right upper lobe of the lung eventually fills the left apical region and obliterates the superior space (Fig. 39). The middle lobe often extends far to the left of the midline to fill the anterior portion of the inferior space. The larger posterior portion of this space (the space between the posteroinferior border of the heart and the costodiaphragmatic sulcus) becomes filled with the enlarged lower lobe, which curiously enough in all the animals examined herniates into the left pleural cavity through the space between the inferior vena cava in front and the vertebral column behind.

The flattening or retraction of the chest wall with its attendant scoliosis invariably appears in animals which have been kept under observation for considerable periods. It does not become evident in the dog until about a month after operation, in other words, at a time when the larger part of the cavity has become obliterated. It progressively increases, and

[9] We may exclude from consideration the cases quoted by other observers in which the tip of a lobe or a single lobe has been removed. In these the obliteration of a small cavity must be very prompt and the presence of fluid even a week or ten days after operation (in the absence of infection) is not to be expected, and is not noted during the days immediately following operation. After the removal of an entire lung a number of observers have commented upon the development of a pleural effusion.

Robinson and Sauerbruch (Deutsche Ztschr. f. Chir., 1909, CII, 542; Centralbl. f. Chir., 1910, XXXVII, I, 391). Of 38 total extirpations performed under positive pressure anesthesia (including those of Haecker) only four animals recovered. In 18 there occurred a marked transudation of clear or slightly turbid fluid into the pleural cavity upon the side of operation, which led in part at least to death. Since in animal experiments carried out under negative pressure this complication did not occur, the authors believed their bad results were due to positive pressure. These authors comment at length on the origin and cause of this transudate, and are convinced that it may occur in the absence of infection.

Schepelman, E. (Arch. f. klin. Chir., 1913, C, 985) states that in dogs the large cavity left after the removal of the lung at first becomes filled with a serous transudate which only later disappears with the obliteration of the cavity.

Other observers have noted the absence of a pleural effusion following total pneumectomy.

Meyer, Willy (J. Am. M. Ass., 1909, LIII, 1978). The autopsy examinations upon four animals of Meyer's series, made by F. C. Wood, showed the following: Dog 1. The left pleural cavity (from which the lung had been removed) showed a small amount of clear serum; Dogs 2, 3 and 4. No fluid in the pleural cavity. (Dogs killed, 10, 13, 18 and 30 days after operation.)

Kawamura, K. (Deutsche Ztschr. f. Chir., 1914, CXXXI, 189), states that, contrary to the experience of Robinson, Sauerbruch and Haecker, he failed to find fluid in the pleural cavity.

[10] Our anticipation of the development of a pleural effusion following experimental pneumectomy is the result of our experience with intrathoracic cavities in man. These have always become filled with fluid; but also have always been infected. The experience with artificial pneumothorax in the treatment of pulmonary tuberculosis shows that, in the absence of infection, large intrapleural cavities as the result of total collapse of the lung persist for months or a year without the development of a pleural effusion.

[11] Kawamura, K.: Experimentelle Studien über die Lungenexstirpation. Deutsche Ztschr. f. Chir., 1914, CXXXI, 189, 222.

in animals kept under observation for seven or eight months is quite marked. It is largely confined to the upper part of the thoracic wall and rarely becomes conspicuous in the lower part of the thorax. While it causes a general diminution in the size of the thorax, it would appear to contribute chiefly toward the obliteration of the superior space (Fig. 41, *A* and *B*, and Fig. 42, *A* and *B*).

The elevation of the diaphragm has not in our experience been an important factor in the obliteration of the pleural cavity in the dog. When present, it contributes toward the obliteration of the inferior space. In the animals studied fluoroscopically the diaphragmatic movements upon the side of operation were, during the period of observation (approximately one month), synchronous with that on the opposite side, and in general of equal amplitude. Occasionally the diaphragm upon the affected side appeared relaxed and lagged behind a little in its movements. In none did the diaphragm occupy a higher position upon the side of operation than upon the contralateral side. In only two animals in the entire series has a spontaneous elevation of the diaphragm occurred following total lobe excision (Figs. 43 and 44). A high elevation of the diaphragm may be produced by division of the phrenic nerve at the time of the pneumectomy, as shown in an X-ray of a dog still living, operated upon by Dr. Holman (Fig. 45). It is interesting to note that even after division of the phrenic, neither cessation of movement nor elevation of the diaphragm occurred in this animal a month after operation. Following the removal of the lung the diaphragm eventually became immobile and occupied a high position.

Reaction of the Remaining Lung to Lobe Excision.—We have just noted that, following the removal of one lung, the remaining lung actually increases in size and that this increase in size contributes in large measure toward the obliteration of the opposite pleural cavity. Is this enlargement of the lung due to a simple dilatation of the alveoli analogous to emphysema or due to a hypertrophy or hyperplasia of the lung? The question is rather of academic than of practical interest. The problem presents many difficulties and will require a repetition of some of our experiments before we can hope to approach its solution. (The material gathered for this purpose was largely lost during our period abroad). From a study of such material as we have, it would appear that in the period immediately following the excision of one lung, the alveoli of the remaining lung are dilated as compared with those of the excised lung. After a period of months, however, they appear much the same as in the control. Whether or not there is an actual increase in size of the main bronchial subdivisions, an increase in the number of the terminal bronchioles, and an actual increase in the number of alveoli per lobule (which could be interpreted as a hyperplasia); or an enlargement of the alveoli with increase in the elastic tissue and an increase in the size and number of the blood vessels (which could be interpreted as a compensatory hypertrophy), all are questions which have not yet been answered.[12] This part of our study may then for the present be dismissed as incomplete.

Longevity of Animals Following Lung Excision.—It seemed to us of interest to determine whether or not total lung excision seriously affected the future life of animals subjected to this operation. A number of the dogs were therefore kept under observation for a year. As soon as they had recovered from the operation they were turned into the yard with other dogs, and were exposed to the same vicissitudes of existence as other animals. So far as we could determine they were active, healthy, free from dyspnea, and held their own with other animals. Only one animal apparently suffered as a result of the removal of the lung. He avoided the other dogs, was not so eager as they at feeding time, and had periodic attacks of dyspnea. With this exception, we could not determine that the excision of one lung affected the activity or the probable duration of life in dogs. One of the animals became pregnant several months after operation and gave birth to a litter of seven healthy pups. This animal is still living.

[12] Kawamura, K. (Deutsche Ztschr. f. Chir., 1913, CXXXI, 189). This author found a dilatation of the alveoli and an increase in the elastic fibers of the remaining lung; later a hypertrophy of the alveoli and a dilatation and increase in number of the blood vessels especially the capillaries—in other words, a true compensatory hypertrophy of the lung. From the description of his technic in the preparation of his material, it would seem that errors in the interpretation of his specimens might well have occurred.

JOHNS HOPKINS HOSPITAL BULLETIN

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXXI is in progress. The subscription price is $3.00 per year.

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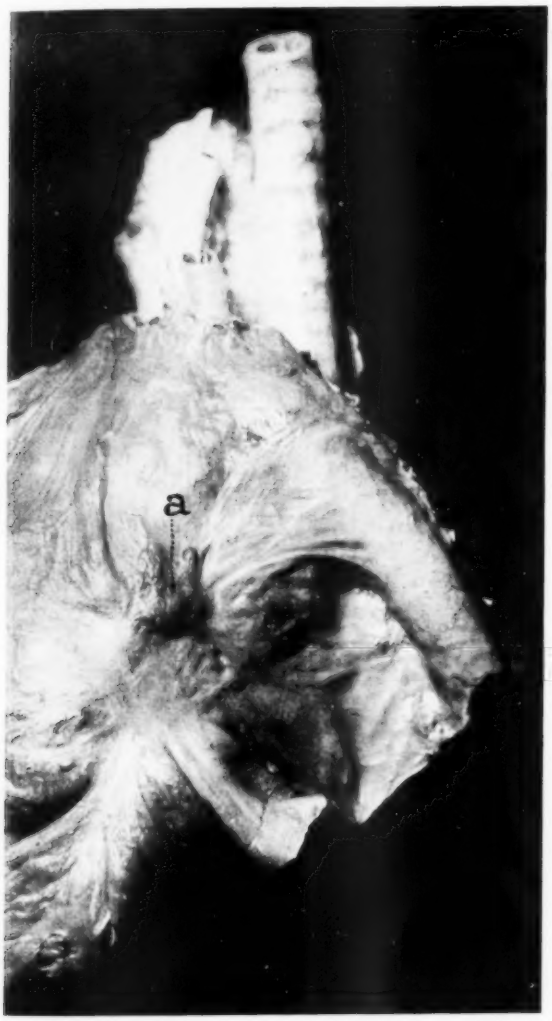

FIG. 2.—Scar (a) upon the mediastinal pleura following a total pneumectomy and indicating the location of the bronchial stump.

FIG. 3B.—A bronchial stump capped by a mass of scar tissue. Treated by Method 1.

FIG. 4.—Mesial section of bronchial stump shown in Fig. 3A, to show the occlusion of the end of the bronchus.

FIG. 3A.—A nicely rounded bronchial stump treated by Method 1.

FIG. 5.—Mesial section of a bronchial stump also treated by Method 1. The bronchial wall has been infolded by the constricting ligature.

FIG. 6.—Mesial section of bronchial stump shown in Fig. 3a, to show occlusion.

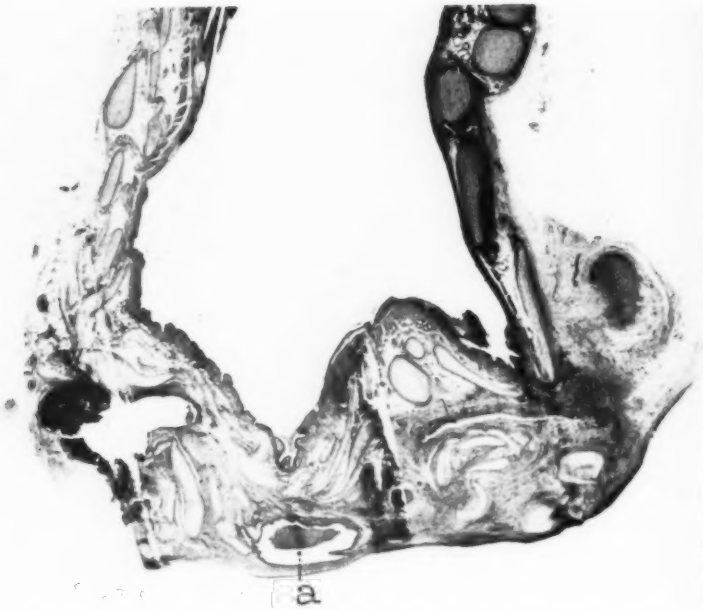

FIG. 8.—Section from specimen shown in Fig. 5. *a*, a cleft lined with mucous membrane.

FIG. 7.—Section from specimen shown in Fig. 4. *a*, a cleft lined by mucous membrane in the occluded end of the stump. *b*, the infolded wall of the bronchus. *c*, silk ligatures.

FIG. 9.—Section from specimen shown in Fig. 6. The marked reaction about the silk ligatures is especially evident in this specimen.

FIG. 10.—Bronchial stump treated by Method 2. The rounded ends of the two subdivisions of the main bronchus are evident in the illustration. Animal sacrificed eight and a half months after operation.

FIG. 11.—Mesial section of specimen shown in Fig. 10.

FIG. 13.—Bronchial stump treated by Method 3.

FIG.—12.—Microscopic section of specimen shown in Figs. 10 and 11. *a*, bronchial wall at the bifurcation of the left main bronchus.

FIG. 14.—Mesial section of bronchial stump shown in Fig. 13.

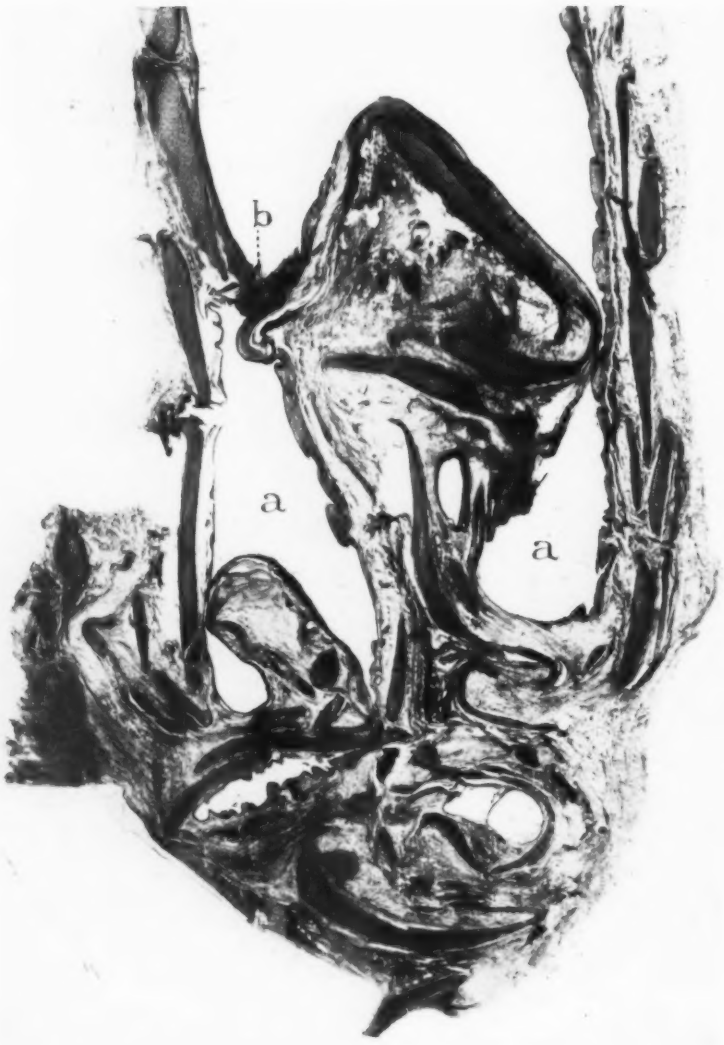

FIG. 15.—Microscopic section of specimen shown in Figs. 13 and 14. *a*, cleft between the invaginated and normal bronchial wall. *b*, point of fusion of mucous membrane of invaginated and non-invaginated bronchial wall.

FIG. 16.—Bronchial stump treated by Method 4.

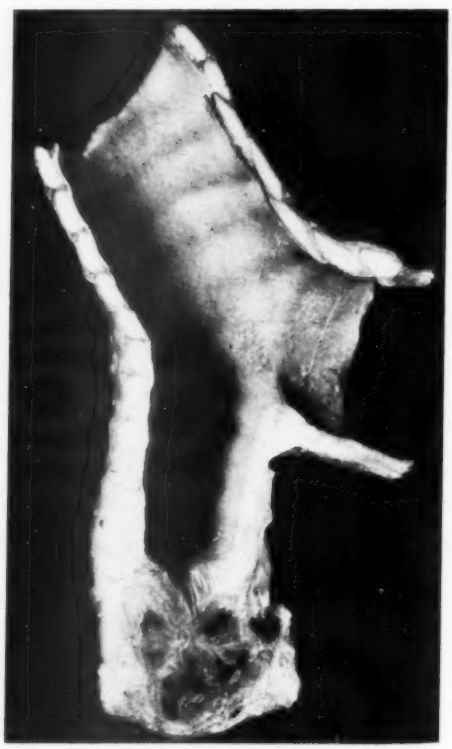

FIG. 17.—Mesial section of bronchial stump shown in Fig. 16.

FIG. 18.—Microscopic section of specimen shown in Figs. 16 and 17.

FIG. 19.—Bronchial stump treated by Method 5 (Willy Meyer), showing bulbous end.

FIG. 20.—Bronchial stump treated by Method 5 (Willy Meyer), showing tapering end.

FIG. 21.—A perfectly healed bronchial stump treated by Method 5. Animal sacrificed three months after operation.

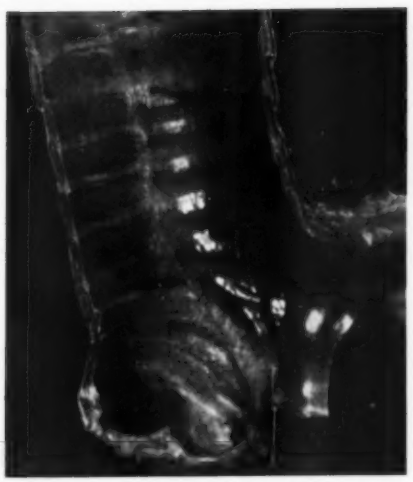

FIG. 22.—Mesial section of bronchial stump treated by Method 5. Animal sacrificed one year after operation.

FIG. 23.—Mesial section of bronchial stump treated by Method 5. The walls of the inverted portion of the stump (*a*) have separated with the formation of a cleft (*b*) between them which communicates with the lemen of the bronchus.

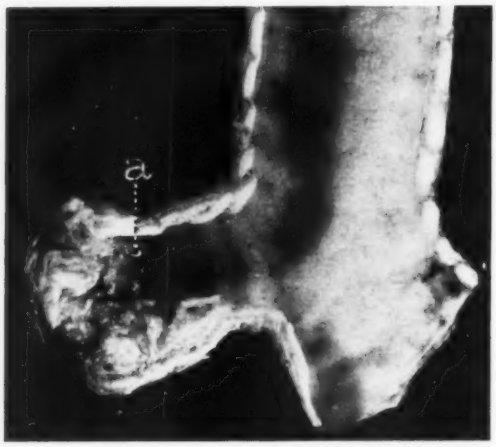

FIG. 24.—Mesial section of bronchial stump treated by Method 5. The cleft between the separated inverted walls of the bronchus (*a*) has become partially filled with scar tissue.

FIG. 25.—Mesial section of bronchial stump treated by Method 5. The short bronchial stump is filled by a mass of tissue which completely occludes it excepting for the cleft at *a*.

FIG. 26.—Microscopic section of specimen shown in Fig. 21.

FIG. 27.—Microscopic section of specimen shown in Fig. 22.

FIG. 28.—Microscopic section of specimen shown in Fig. 23. *a*, cavity or cleft between inverted walls of bronchus.

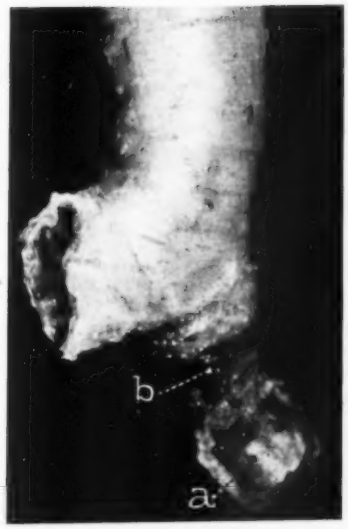

FIG. 31.—Bronchial stump treated by Method 6. *a*, metal band. *b*, necrosis with perforation of bronchial wall.

FIG. 29.—Microscopic section of specimen shown in Fig. 24.

FIG. 30.—Microscopic section of specimen shown in Fig. 25. *a*, silk ligature.

FIG. 32.—Mesial section of specimen shown in Fig. 31. The metal band has been removed. *a*, solid cord of tissue under metal band. *b*, perforation of bronchus above band.

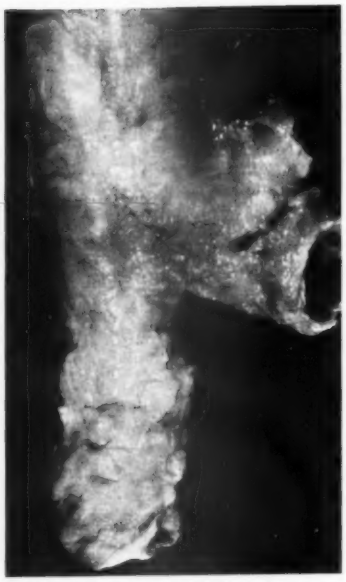

FIG. 34.—Bronchial stump treated by Method 6.

FIG. 33.—Microscopic section of solid cord of tissue shown in Fig. 32, *a*. The mass is made up largely of cartilage, the cells of which largely fail to stain.

FIG. 35.—Mesial section of specimen shown in Fig. 34. *a*, metal band covered entirely by fibrous tissue. Beneath the band is a solid cord of tissue.

FIG. 36.--Microscopic section of specimen shown in Figs. 34 and 35. *aa*, space occupied by metal band; *b*, solid cord of tissue beneath band; *c*, fibrous tissue covering band. The metal band has not cut through the bronchial wall. Animal sacrificed six months after operation.

FIG. 37.—X-ray of animal seven months after a total left pneumectomy. The upper part of the heart is in contact with the thoracic wall. There is marked retraction of the upper thorax. The diaphragm is not elevated. The triangular space, bounded by the heart, diaphragm and thoracic wall, appears to be a true space, as seen with the fluoroscope; but is probably occupied by the lower lobe of the right lung.

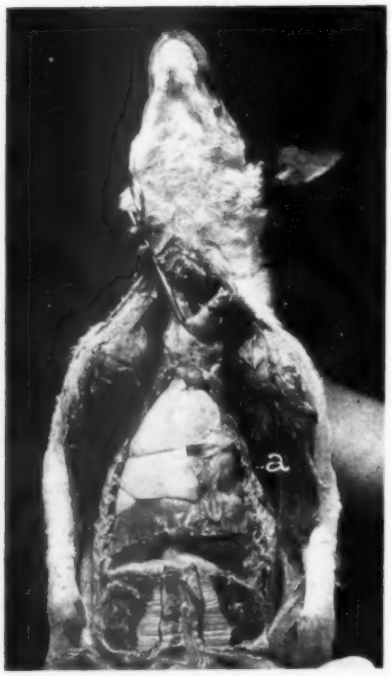

FIG. 39.—Thoracic organs of an animal sacrificed five and a half months after a left total pneumectomy. The left pleural cavity is completely obliterated excepting for the cleft at *a*.

FIG. 38.—Thoracic organs (fixed *in situ*) of an animal sacrificed three months after a total left pneumectomy. The heart is in contact with the thoracic wall. The right lung has enlarged and extended toward the left. The left pleural cavity is completely obliterated excepting for the cleft at *a*.

FIG. 40.—Thoracic organs of an animal sacrificed seven and a half months after a total left pneumectomy. The left pleural cavity is completely obliterated.

FIG. 41A.—Animal five and a half months after a total left pneumectomy. The flattening of the thorax is not conspicuous.

FIG. 41B.—Same animal as in Fig. 41A. After exposure of the bony thorax the flattening of the chest upon the left side is evident.

FIG. 42A.—Animal about one year after a total left pneumectomy. The flattening of the chest is inconspicuous.

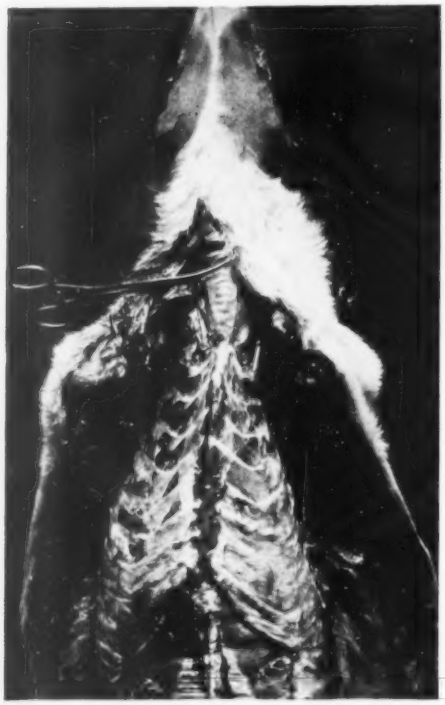

FIG. 42B.—Same animal as shown in Fig. 42A. The flattening of the chest after exposure of the bony thorax is evident.

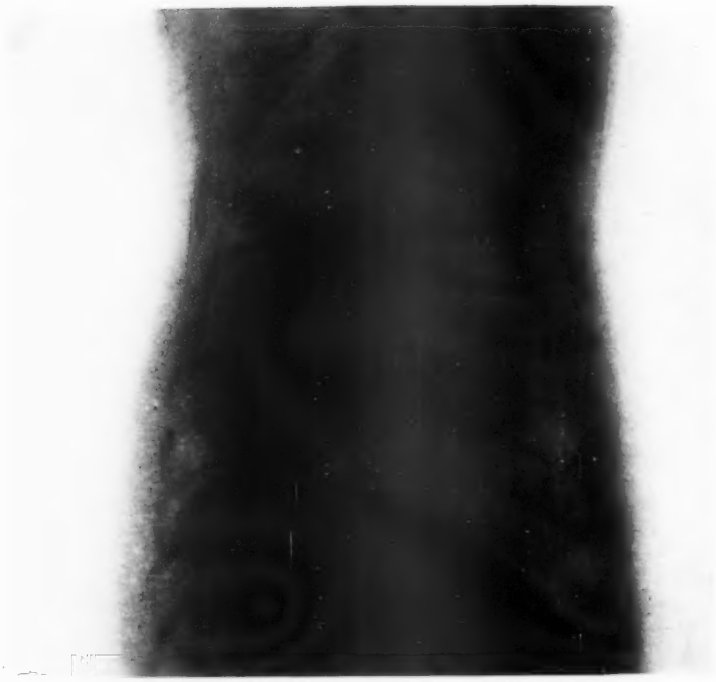

FIG. 45.—Elevation and immobility of the diaphragm seven months after a left total pneumectomy combined with division of the phrenic nerve.

FIG. 43.—The diaphragm seven and a half months after a total left pneumectomy. There is no elevation of the diaphragm on the pneumectomized side; the usual finding in our experience.

FIG. 44.—The diaphragm in an animal sacrificed five and a half months after a total left pneumectomy. The diaphragm is markedly elevated on the side of operation. It is one of only two instances in which elevation of the diaphragm was noted.

THE EFFECT OF ARTERIOVENOUS FISTULA UPON THE HEART AND BLOOD-VESSELS

AN EXPERIMENTAL AND CLINICAL STUDY

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Since the fall of 1914 it has been my good fortune to make with Professor William S. Halsted some experimental and clinical observations upon the blood-vessels and heart. Some of these studies [1] have been reported in detail, while references [2] to the results of observations have been made. The work was begun by studying the effect of partially occluding aluminum bands upon the larger arteries of dogs, and was stimulated by some clinical observations upon subclavian ribs, which, when they partially occluded the subclavian artery, sometimes gave rise to the formation of an aneurysm just distal to the rib. Thus begun, our work has led into various other lines. One of these was to study experimentally the effect of arteriovenous fistula on the vascular system.

Dr. Halsted was familiar with the fact that an arteriovenous fistula altered materially the size of the artery proximal and distal to the point of fistula, and had seen clinical cases in which the heart was markedly dilated and hypertrophied. With his idea in mind that the same cause might explain the two clinical observations, namely, that an artery dilates distally to a partial occlusion of its lumen, and proximally to an arteriovenous fistula, I began producing fistulæ between the arteries and veins of dogs. This work has been invaluable surgical practice, and has allowed me to make some observations which I believe are sufficiently interesting to justify their record.

At first, fistulæ were made between the femoral artery and vein, but these usually did not remain patent for a longer time than a few months. When the internal carotid artery and jugular vein were used there was no difficulty in getting the fistula to remain permanently patent.

The technique employed for producing the arteriovenous fistulæ is described by Carrel.[3]

[1] Halsted and Reid: An experimental study of circumscribed dilatation of an artery immediately distal to a partially occluding band, and its bearing on the dilatation of the subclavian artery in certain cases of cervical rib. Partial occlusion of the aorta with the metallic band. Observations on blood pressures and changes in the arterial wall. J. Exp. Med., 1916, XXIV, 271, 287.

[2] Halsted, W. H.: Cylindrical dilatation of the common carotid artery following partial occlusion of the innominate and ligation of the subclavian. Surg. Gynec. and Obst., 1918, XXVII, 547.

Halsted, W. H.: Congenital arteriovenous and lymphaticovenous fistulæ. Unique clinical and experimental observations. Proc. Nat. Acad. Sc., Balto., 1919, V, 76 and Trans. Amer. Surg. Assoc., 1919.

[3] Carrel, A.: Johns Hopkins Hosp. Bull., Balto., 1907, XVIII, 18.

EXPERIMENTS

The observations on Dog 9 are the most complete and really form the basis of the experimental study, but in order to draw attention to some points which this animal did not show, I will include short abstracts of all of the experiments.

Dog. 1.—December 10, 1914. A fistula was made between the right femoral vein and artery. There was never a thrill nor a bruit present over the fistula, but an arterial pulse could be felt on both sides of it.

March 24, 1915. A second fistula was made between the right external jugular vein and the internal carotid artery. This fistula remained permanently patent and at its site there were always a distinct thrill and a loud continuous bruit.

May 17, 1915. Animal found dead. No apparent cause for death. The fistula in the neck was patent. The vein distal to the anastomosis was markedly dilated, proximally it was collapsed and very small. No change in the artery on either side of the fistula could be detected. Between the femoral vessels the fistula had closed, the lumina of the vessels remaining patent. Below the anastomosis the artery seemed slightly smaller than above it.

Dog. 2.—December 21, 1914. A very small dog. A fistula was made between the right femoral vessels. At the time of the operation a distinct thrill and bruit were present. At no time following the operation was there evidence that the fistula was open. On account of distemper the animal was sacrificed on January 27, 1915. The fistula was closed and the lumen of the artery was occluded at the point of anastomosis. No thrombus on either side of the occlusion. The lumen of the vein was patent.

Dog 3.—January 4, 1915. Fistula made between the right femoral vessels. For two and one-half months the thrill and bruit persisted. Their disappearance was gradual.

May 19, 1915. Animal sacrified. The fistula was closed by a thin membrane lined on either side by intima. At the periphery of this new membrane the continuous silk suture was visible. Both artery and vein were patent and there was no thrombosis. There was no apparent dilatation of the artery or vein on either side of the anastomosis.

Dog 4.—January 26, 1915. Large dog. Fistula made between the right femoral vessels. The leg became markedly swollen and did not return to its normal size until about two weeks after the operation. Superficial veins became prominent soon after the operation and then gradually decreased in size.

A marked thrill and bruit were present over the fistula for several months. On May 20, 1915, a small expansile swelling about half the size of a cherry was noted at the site of the fistula. Thrill and bruit were still present, but not so marked. The swelling grew larger and the signs of a fistula less pronounced, until on August 9, 1915, the swelling was the size of a cherry and had the characters of a simple aneurysm, the continuous thrill and bruit having disappeared. The aneurysm remained present but decreased somewhat in size after the fistula had closed.

June 4, 1916. Dog sacrificed. At this time, about 16 months after the fistula had been produced, the vein was found to be totally occluded by a rounded swelling which projected from the artery into the lumen of the vein. A false membrance which had closed the fistula had apparently given way to the tension of the arterial blood and thus formed the little saccular aneurysm. There was no thrombus. The artery was slightly larger on the proximal than on the distal side of the fistula. The vein, proximal and distal to the point of its occlusion by the aneurysm, was collapsed, but its lumen was not obliterated except at the site of the aneurysm.

Dog. 5.—February 2, 1915. A fistula was made between the right femoral vessels. Twenty days later the dog died of pneumonia. The fistula was patent. There was no alteration in the size of the artery. The vein was dilated distal to the fistula.

Dog 6.—February 16, 1915. Fistula made between the right femoral vessels. The thrill and bruit persisted for about two months after the operation.

May 19, 1915. Dog sacrificed. The fistula was closed by a thin septum covered by intima on both sides. Both artery and vein were patent; neither was dilated.

Dog 7.—February 2, 1915. A fistula was made between the external jugular vein and the internal carotid artery of the right side of the neck. A marked thrill and loud bruit were always present.

March 5, 1915. Dog sacrificed. Fistula patent. The artery on either side of the anastomosis was not dilated. The vein distal to the anastomosis was markedly dilated, centrally the dilatation was slight.

Dog 8.—February 22, 1915.—A right carotico-jugular fistula was made. It remained open. No change in the appearance of the dog's head or eyes occurred.

June 24, 1915. Animal sacrificed. A continuous thrill and bruit were very pronounced. Distally to the fistula the vein was markedly dilated; proximally the dilatation was less. The diameter of the artery was increased on the proximal side of the fistula, while on the distal side it measured the same as before the operation.

Dog 9.—February 26, 1915. Weight 14 pounds. Fistula made between the right external jugular vein and the internal carotid artery.

For 30 months frequent observations of this dog were made. A marked thrill and a loud continuous bruit with systolic intensification were always present at the site of the fistula. Toward the end of the observations it was evident that the artery proximal to the fistula was dilated and the vein, distally, dilated up to the mandible. Facial asymmetry or change in the eyes did not occur.

The heart at first was normal; later it became enlarged and irregular in action. A cardiac murmur developed and a thrill was felt over the precordium for a few weeks before death. An electrocardiogram was made on October 13, 1916, and again on October 10, 1917 (Figs. 1 and 2).

Roentgenograms of the heart were made in the falls of 1916 and 1917 (Figs. 3, 4 and 5).

On October 29, 1917, this dog was found dead in his cage. A copy of the autopsy dictation is here given.

The dog weighs 14½ pounds. No apparent cause of death is found either externally or in any of the cavities of the body.

The fistula is patent. The right carotid artery is deflected laterally, leaving the right vagus with an enlarged accompanying vein mesially. The left carotid artery is normal, but the left jugular vein is very large and the transverse anastomotic branch above the cricoid is huge. The artery on the proximal side of the anastomosis is much larger than on the distal side. This dilatation is apparent in the undistended artery and extends back to the aorta. When the arterial system is distended by injecting fluid into the aorta the difference is even more striking, the artery central to the anastomosis distending more than on the peripheral side. The right jugular vein is markedly dilated distal to the fistula, whereas, central to it, it is possibly smaller than normal (Fig. 6).

The heart in this case appears definitely enlarged, both *in situ* and after removal. The right ventricle is certainly thicker than normal. The valves are normal. Weight of heart, 160 gm.; tricuspid valve measures 8.75 cm.; pulmonary,

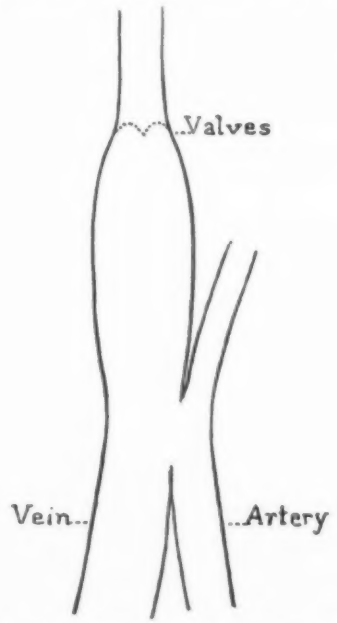

Fig. 10.—Dog. 10. External jugular vein and carotid artery, 4 months after the making of the fistula. Magnified 2 times. Note the proximal dilatation of the artery.

4.5 cm.; mitral, 7.0 cm.; aortic, 4.0 cm.; wall of left ventricle, 1.0 cm.; of right, 0.5 cm.

Dog 10.—February 5, 1915. Right carotico-jugular fistula made. Observations covered a period of four months and ten days.

June 16, 1915. Animal sacrificed under ether thus permitting observations on the vessels in life. Accurate measurements of the size of the vessels were made. The artery was dilated proximal to the fistula. Distally the vein was dilated to its first value, a distance of about 2 cm. Beyond this it was of normal size, but pulsated. Proximally, the vein was somewhat dilated to the clavicle. On opening the vessels we observed that the first valve distal to the fistula was sagged and hypertrophied but not broken. The anastomosis measured 2 mm. in diameter. No thrombosis.

Dog 11.—February 5, 1915. Fistula made in the right side of the neck. Thrill and bruit disappeared gradually in 40 days.

June 24, 1915. Dog sacrificed under ether. On both sides of the fistula the vein was collapsed. The edges of the fistula were attached to the opposite wall of the vein. There was no thrombosis in either vessel. The artery was normal.

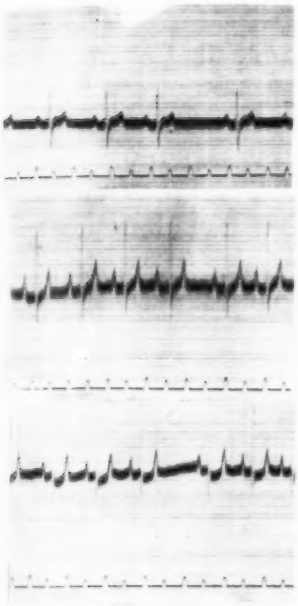

FIG. 1.—Electrocardiogram of dog 9, October 13, 1916. A fistula between the carotid artery and external jugular vein had been present for 20 months.

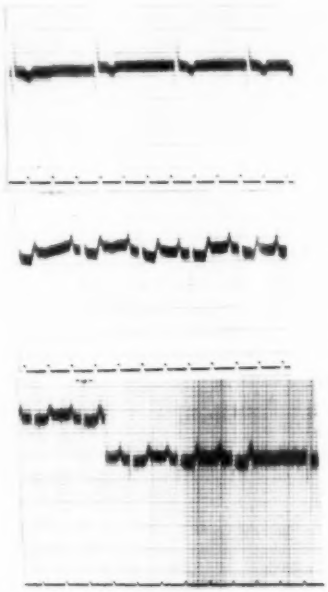

FIG. 2.—Electrocardiogram of dog 9, 12 months later.

FIG. 3.—Roentgenogram of the heart of a normal dog weighing 17½ pounds.

FIG. 4.—Roentgenogram of the heart of dog 9, 20 months after the fistula was produced. Weight of dog 14 pounds.

FIG. 5.—Roentgenogram of dog 9, 32 months after the fistula was produced. Note the increase in size of the heart. Weight of heart, 160 grams.

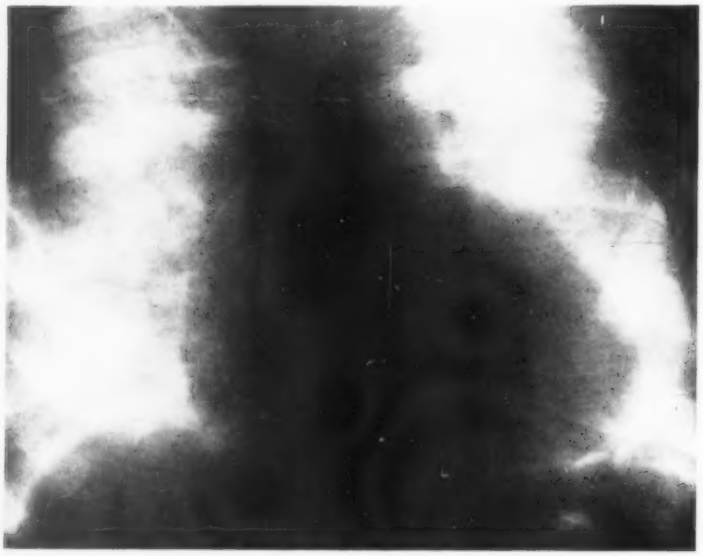

FIG. 7.—Roentgenogram of the chest of Case 1. Arteriovenous fistula between the femoral vessels had been present for many years (*vide* Fig. 8). Note the enormous size of the heart.

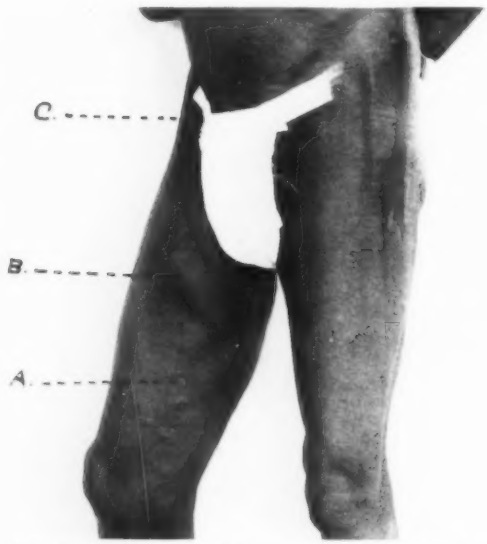

FIG. 8.—Photograph of Case 1. *A*, scar opposite the arteriovenous fistula. The entire artery proximal to the fistula is markedly dilated. At *B* and *C* the dilatations were so marked that they resembled saccular aneurysms. The heart of this patient was very large (*vide* Fig. 7).

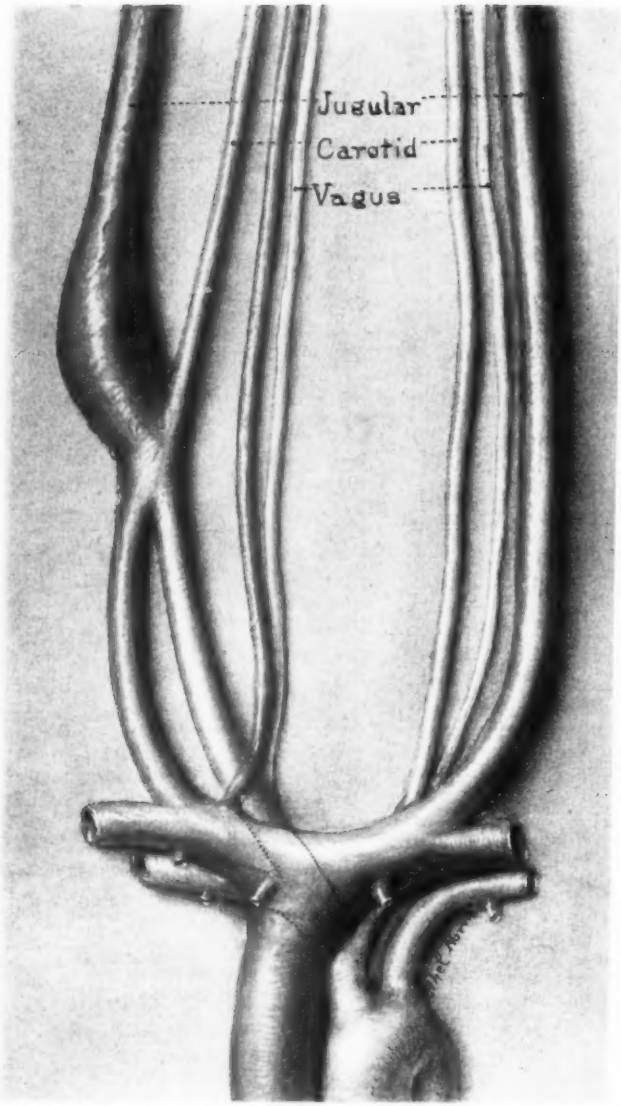

FIG. 6.—Dog 9. Actual size of the vessels distended by an equal pressure. A large accessory vein has developed by the right vagus nerve. Left jugular vein is large. Carotid artery dilated, from the arch of the aorta to the fistula. The vein proximal to the fistula was not markedly dilated, but its wall showed the most marked hypertrophy of the elastic tissue. Duration of fistula 32 months.

FIG. 9.—Actual size specimen of Case 3. An aneurysmal dilatation of the artery apposite the fistula. The artery is dilated proximally.

DOG 12.—February 5, 1915. Fistula made in the right side of the neck. The thrill and bruit remained present, but diminished markedly in intensity.

June 13, 1915. Animal sacrificed. The original fistula was closed by a thin diaphragm in the center of which was a very small opening which united the lumina of the two vessels. The artery was not dilated on either side of the fistula.

CLINICAL STUDY

Since the opening of The Johns Hopkins Hospital 14 cases of arteriovenous fistula have been admitted to its wards. Of these, some are so unusual and interesting that they will later be published in detail. For purposes of discussion and correlation of the clinical cases with the experimental work, short abstracts of all the cases are here given. They are studied with particular reference to the effect of the fistula upon the artery and the heart.

CASE 1.—Surgical No. 41803. A negro man of 48, was admitted October 13, 1916, with an arteriovenous fistula in Hunter's canal, on the right side. In his past life he could recall no incident that might have caused his condition. However, a very definite round scar was present in the skin just opposite the point of fistula. The patient knew that for several years, at least three, he had had a swelling in the right thigh and had observed it beating against the covers of his bed. What had brought him to the hospital was a sudden sharp pain 10 days before admission. As regards the leg, the patient said that he had paid no attention to the swelling for he thought that everybody may have had the same thing. In his past history it was interesting to note that at the age of 25 he had had a severe hemorrhage from the urethra. The bleeding continued for eight days and following this he was in bed seven weeks. Eight years before admission a small wound on the shin of the right leg bled profusely for seven days. Five years before admission he had bled severely from a small wound of the right foot. I mention these points as evidence that the patient had probably had a fistula for years. The artery proximal to the fistula was hugely dilated and tortuous (Fig. 8). The dilatation extended above Poupart's ligament to the abdominal aorta. The heart was enlarged, extending 13 cm. to the left of the midline and 4 cm. to the right. There was a slight precordial heave and a wide area of retromanubrial dullness associated with a definite tracheal tug. There was a definite blowing systolic murmur at the apex well transmitted to the axilla. There was also a very definite forcible pulsation in the epigastric region. The Wassermann reaction was negative. *Fluoroscopic examination of the chest showed that the entire aorta was very much enlarged.*[1]

At the operation performed October 31, 1916, by Dr. Halsted, the fistula was divided and the openings in the artery and vein were closed by lateral sutures of silk. On the proximal side of the

[1] Dr. Admont Clark made observations on the venous pressures of this patient both before and after operation: Before operation, right calf 19.5 cm. water; left calf 7.0 cm. water. Two months after operation, right calf 15 cm. water, left calf 15 cm. water. He regarded the pressures obtained two months after operation as normal.

TABLE 1.—A SUMMARY OF THE ANIMAL EXPERIMENTS

Dog	Position of fistula	Duration of experiment	Duration of fistula	Proximal dilatation of artery	Effect on heart	Remarks
1	Carotid artery and external jugular vein.	1 month, 23 days.	1 month, 23 days.	No.	Not noted.	
2	Femoral vessels.	1 month, 6 days.	4 (?) days.	No.	Not noted.	First observation was made a week after the operation. Fistula was then closed.
3	Femoral vessels.	4 months, 15 days.	2 months, 15 days.	No.	Not noted.	
4	Femoral vessels.	17 months, 10 days.	6 months.	Slight.	Not noted.	In this case the proximal dilatation may have decreased some in size after the fistula closed.
5	Femoral vessels.	18 days.	18 days.	No.	Not noted.	
6	Femoral vessels.	3 months.	2 months.	No.	Not noted.	
7	Carotid artery and external jugular vein.	1 month, 3 days.	1 month, 3 days.	No.	Not noted.	
8	Carotid artery and external jugular vein.	4 months.	4 months.	Moderate.	Not noted.	The dilatation was confirmed by careful measurements made at time of operation and when dog was sacrificed.
9	Carotid artery and external jugular vein.	33 months.	33 months.	Striking.	Heart markedly enlarged.	Death believed to be due to cardiac condition.
10	Carotid artery and external jugular vein.	4 months, 10 days.	4 months, 10 days.	Very definite.	Not noted.	
11	Carotid artery and external jugular vein.	4 months, 19 days.	1 month, 10 days.	No.	Not noted.	
12	Carotid artery and external jugular vein.	4 months, 13 days.	4 months, 13 days.	No.	Not noted.	In this case the fistula was almost completely closed when the dog was sacrificed.

fistula the artery was enormously dilated and showed a tendency toward sacculations, while on the distal side it was no larger than normal. There was a definite arteriosclerosis.

Case 2.—Surgical No. 44386. A negro man of 48 years was admitted October 2, 1917. In the left thigh there was an arteriovenous fistula which had resulted from a pistol-shot wound received 12 years before admission. The typical signs developed immediately after the accident. For two years following the accident he did hard work and was not troubled except at times with a little shortness of breath and some pain in the abdomen. These symptoms were probably first noticed by the patient six months following the injury. For the next nine years the patient did light work but was bothered a great deal with increasing shortness of breath and swelling of the left leg. For the six months previous to admission his cardiac symptoms had become so marked that he had spent most of his time in bed.

The typical physical signs of an arteriovenous fistula at the apex of Scarpa's triangle were present. The artery proximal to the point of fistula was definitely dilated and could be traced with almost certainty up to the bifurcation of the aorta. The impression of this patient's condition on the medical service was chronic myocarditis, auricular fibrillation, myocardial insufficiency and marked cardiac dilatation. It was suggested that arteriosclerosis might be the cause of the heart trouble. The Wassermann reaction was negative and there was no history of syphilis; nor could there be obtained any history of rheumatism or frequent sore throats. To me it was very interesting to note that the cardiac symptoms began to develop several months after the arteriovenous fistula was produced. The cardiac condition was so bad that we did not operate on this patient.

The report of the electrocardiogram was: Auricular fibrillation.

Case 3.—Surgical No. 6550. A laborer, 34 years old, was admitted May 21, 1897, with an arteriovenous fistula in the left popliteal space. In his past life there was a history of alcoholism and possibly a luetic infection. The Wassermann reaction was not made. The fistula had resulted from a bullet wound received eight years before admission. The signs of the fistula had developed immediately after the accident. He came to the hospital on account of swelling of his leg and localized attacks of acute pain over his heart.

The typical physical signs of an arteriovenous fistula were present. The heart was enlarged to the ninth rib on the left side. A blowing systolic murmur was present. The liver extended 2 cm. below the costal margin.

At the first operation, June 12, 1897, by Dr. W. S. Halsted, the artery proximal to the fistula was ligated. On account of gangrene due to the *B. welchii*, the leg was amputated. The specimen (Fig. 9) which had been preserved in alcohol for 20 years shows that the artery is dilated proximal to the fistula and that there is a little aneurysm of the artery just opposite to it. The sections of these vessels show an increased amount of elastic tissue in the vein, while the difference in the elastic tissue of the artery on the two sides of the fistula is not striking. The aneurysm of the artery has no elastic tissue in its wall (Plate XXV). The hypertrophy of elastic tissue in the vein seems to be more marked on the proximal than on the distal side of the fistula.

Case 4.—Surgical No. 27731. A blacksmith, aged 55, was admitted February 9, 1911, with an arteriovenous fistula just below the right Poupart's ligament. Four months previously a piece of flying steel had produced the fistula. The heart was not enlarged and the sounds were clear.

On February 7, 1911, the vein proximal to the site of the fistula was ligated. No mention of an arterial dilatation on either side of the fistula was made. No marked changes in the physical signs of the fistula resulted from the operation.

About a month after the operation the patient had a severe attack of dizziness and vertigo, associated with nausea and vomiting. The heart then measured 12.5 cm. to the left of the midline in the fifth interspace; to the right it came to the sternal margin.

January 2, 1918. His physician writes that the patient is working at his trade. The fistula is still patent; the superficial veins in the leg are larger and a small ulcer has developed over the shin. No cardiac symptoms are mentioned.

Case 5.—Surgical No. 32461. A negro man, 47 years old, admitted July 7, 1913, complained of numbness in the left leg and an enlarged artery.

Thirty years before admission he had been shot in the left thigh and groin with a shotgun. Following this accident the patient was perfectly well until two years before his admission when he noticed a throbbing and fluttering in his groin. A month later he noticed that his left leg tired easily and he began to walk with a definite toe drop. There was never any marked swelling of the ankle nor of the leg.

On examination the typical signs of an arteriovenous fistula were present. The heart was not enlarged.

At the operation, July 5, 1913, lateral sutures of the femoral artery and vein were made. The artery proximal to the fistula was markedly dilated while distal to it, it seemed to be contracted. The patient died from pneumonia and empyema three weeks after the operation. The operative result was excellent.

At autopsy the heart weighed 320 gm. and was normal. The artery proximal to the point of fistula measured 4 cm. in diameter and was about two times as large as the normal vessel. This dilatation did not extend to the aorta.

Case 6.—Surgical No. 12721. A man, 19 years of age, was admitted November 26, 1901, three months after a stab wound which had resulted in an arteriovenous fistula in the left thigh. At that time his heart was normal. He was operated upon December 6, 1901. The femoral artery was ligated and the opening in the vein was sutured. At this time the vessels were noted to be small and no dilatation of the artery was present on either side of the fistula. The heart was not enlarged.

He returned January 5, 1906, five years later, complaining of weakness in the left leg. The symptoms had developed in the six weeks preceding this admission. These were extreme weakness and difficulty in walking. The aneurysm was completely healed and there was no evidence of swelling of the leg. A pulse could be felt in the left posterior tibial artery. The blood pressure in the left leg was 65 and in the right 100. The diagnosis was intermittent claudication. The heart was normal.

Case 7.—Surgical No. 21965. A white man, 55 years of age, was admitted on February 12, 1908, for an arteriovenous fistula in the palm of the right hand. He had been struck in the palm of his hand 25 years before admission by a broken axe handle. Not until five years later did the accident bother him, but then a swelling appeared at the base of the right index and middle fingers. This swelling gradually increased in size. Pulsation had been noted for 15 years, but no pain until two weeks before coming to the hospital, when from a slight injury his hand became painful and bled.

Physical examination showed his heart to be not markedly, if at all, enlarged and the second sound was accentuated all over the heart. Marked thrill and continuous bruit were present in the swelling of the hand.

At the operation the fistula was excised. No mention is made of arterial dilatation. The patient was discharged well.

Case 8.—Surgical No. 17168. A white man, aged 23, was admitted on December 26, 1904, for an arteriovenous fistula in the palm of the hand, particularly at the base of the middle finger. The symptoms had begun 10 years previously without any evident injury, unless they were caused by playing baseball.

The heart was not enlarged. A thrill and bruit were present in the hand. The radial artery was ligated and the vessels in the palm of the hand were partially excised. No note was made as to whether the artery was dilated. He was discharged improved.

CASE 9.—Surgical No. 13260. A carpenter, age 24, was admitted with a fractured base of the skull, on April 17, 1902. A decompression was done and a ruptured middle meningeal artery was litigated. The presence of a fistula was not suspected.

About six weeks after this operation the patient returned with a severe pain and roaring in the right side of his head. He described the noise as like that of a canary bird singing. An anteriovenous fistula was again not suspected.

May 5, 1905 (three years after the last admission), the patient returned complaining of a protrusion of the right eye and a buzzing in the head. These symptoms had gradually been getting worse since his fracture of the skull three years before. For six weeks before this admission the noise in his head, the double vision and the exophthalmos, had become so bad that he could not work. There was a remarkable pulsating exophthalmos of the right eye, a definite thrill over the entire head and a continuous murmur with systolic intensification, and a marked dilatation of the veins around the eye. The heart was normal except for a slight irregularity.

May 9, 1905. The right internal carotid artery was ligated. No note as to the size or appearance of this vessel was made. For about 15 minutes following the ligation, which was done under cocaine, the exophthalmos diminished, the arteries in the fundus became less distinct, and the thrill and noise were gone. The exophthalmos quickly returned and became even more marked than before the ligation. Other symptoms quickly returned and the patient left the hospital on May 26 unimproved.

June 17, 1907, the patient again came into the hospital with the same old symptoms, even more severe. It was noted then that the veins of the eyelid and forehead were not so large as previously. The bruit over the eye and head was less distinct. Double vision was still present. Nothing was done.

January 1, 1909, the bruit was very difficult to hear (only in front of the ear); there was very little exophthalmos; the right eye was turned by a total abducens palsy; there was no dilatation of the veins of the forehead; and the patient still heard the bruit. He was working, and in good health.

July 20, 1911, the exophthalmos was gone and the patient felt well except for headaches.

CASE 10.—Surgical No. 42514. A white man, 48 years old, was admitted April 7, 1917, with the symptoms and signs of an intracranial arteriovenous fistula. Pulsating exophthalmos was present. The symptoms had developed following a fractured skull in February, 1916. The heart was normal.

At the operation, April 18, 1917, it was noted that the internal carotid artery was unusually tortuous, but no comment was made upon the size of this vessel.

CASE 11.—Surgical No. 45360. A negro man, age 55, was admitted on March 9, 1918, for pulsating exophthalmos, due to an intracranial arteriovenous fistula. The symptoms had developed following a fracture of the base of the skull two and one-half months before admission. The case is remarkable and deserves to be made the subject of a special report. It is mentioned here to draw attention to the fact that the carotid artery at operation did no appear to be dilated. The patient's heart was not enlarged and was apparently normal.

CASE 12.—Surgical No. 18104. Male, age 31, white, was admitted August 7, 1905, for an arteriovenous fistula between the left occipital vessels. Seven years previously his head had been injured. The swelling and noise had appeared about two months after the accident. He had been operated upon four months before admission to this hospital, the occipital artery being ligated. There was improvement, but the typical symptoms of a fistula remained. The external carotid artery was ligated August 9, 1905, and also many of the anastomotic branches leading into the varix. No mention is made of any dilatation of the carotid artery or of any abnormality of the heart.

CASE 13.—Surgical No. 28688. A white girl, at the age of 11, was admitted November 3, 1911, to this hospital for a congenital arteriovenous fistula in the right side of the neck. The heart was not enlarged. The external carotid artery proximal to the fistula was dilated. Ligation of this vessel improved but did not cure her.

At the age of 18, May 15, 1918, she returned with the fistula and symptoms about the same as at the first operation. The heart was still not enlarged. Another artery proximal to the fistula had become markedly dilated.

CASE 14.—Surgical No. 46583. A white boy, aged 18, admitted to the hospital on September 17, 1918. In the right side of his neck was an arteriovenous fistula associated with an enormous angiomatous dilatation of the veins. It had been present for five years and had developed without any apparent cause. From the character of the aneurysm and the appearance of the vessels about it, we were inclined to believe that it was a congenital arteriovenous connection. His heart was normal.

At operation a dilatation of the carotid artery was not evident; the innominate artery was not seen.

DISCUSSION

When the experiments were begun I was not familiar with the clinical observations in regard to the effect of an arteriovenous fistula on the artery. In fact I had thought that, as in the cases of cervical ribs, the artery might dilate distally to the fistula. A few months later it was my good fortune to help Professor Halsted to operate upon a long standing case of arteriovenous fistula (Case 1). The artery was markedly dilated for a long distance proximal to the fistula. This observation lead to a study of the literature in which were found numerous similar observations. Then we began to wonder if we might not in animals obtain experimentally results similar to those that had been observed in human beings.[5]

After keeping one dog for nearly three years we were pleased to find that there had been produced experimentally, for the first time, the clinical observations. In Dog 9 (Fig. 6) the artery proximal to the fistula was markedly dilated. Yet it was only toward the end of this period that it was possible to observe this by palpation. Dog 10 was kept for a period of four months and ten days, and in him a slight proximal dilatation was noted (Fig. 10). These observations agree with the clinical history of cases in human beings; namely, that it takes years for the artery to dilate proximal to an arteriovenous fistula. Distal to the point of fistula the artery gradually becomes a little smaller than normal.

I was impressed by the frequency with which experimentally produced arteriovenous fistulæ close spontaneously. The fistulæ between the femoral vessels invariably closed after a period of several months, while those in the neck usually remained patent indefinitely. The fistulæ usually became

[5] A complete study by Dr. C. L. Callander of all the reported cases of arteriovenous fistula will soon appear. In this report the literature will be given fully.

TABLE II.—A SUMMARY OF THE CASES OF ARTERIOVENOUS FISTULA; ADMITTED TO THE JOHNS HOPKINS HOSPITAL

Case	Age	Position of fistula	Etiology	Symptoms	Duration of fistula	Effect on artery	Effect on heart	Remarks
Surgical No. 41803.	48	Hunter's canal.	Trauma, but history of it unobtainable.	Swelling and pain in leg.	Probably many years.	Marked proximal dilatation extending to heart.	Enlarged.	Wassermann reaction was negative. Fistula probably was present for 20 to 30 years.
Surgical No. 44386.	48	Scarpa's triangle.	Pistol shot.	Shortness of breath and swelling of leg.	12 years.	Marked proximal dilatation.	Extremely large and decompensated.	Neither in the history nor the physical findings was there anything other than the fistula to explain the cardiac condition.
Surgical No. 6560.	34	Popliteal space.	Pistol shot.	Swelling and pain in leg. Pain over heart.	8 years.	Definite proximal dilatation.	Markedly enlarged.	The leg had to be amputated on account of infection.
Surgical No. 27321.	55	Femoral region.	Piece of flying steel.	Pain in the hip and swelling of leg.	4 months.	Not noted.	Possibly slight.	A month after the operation which did not cure the patient the heart was noted to be slightly hypertrophied.
Surgical No. 32461.	47	Femoral region.	Gunshot wound.	Weakness in leg and toe-drop.	2 years and probably longer.	Marked proximal dilatation.	None.	At autopsy the heart was normal. The dilatation in the artery did not extend up to the bifurcation of the aorta.
Surgical No. 12721.	19	Femoral region.	Stab wound.	Pain and a "noise in groin."	3 months.	No dilatation.	None.	
Surgical No. 21965.	55	Hand.	Injury by handle of an axe.	Pain, swelling and noise.	20 to 25 years.	Not noted.	"Not markedly if at all enlarged."	
Surgical No. 17168.	23	Hand.	Injury by base-ball.	Swelling and pain.	10 years.	Not noted.	Not enlarged.	
Surgical No. 13260.	24	Intracranial.	Fracture base of skull.	Pain and noise in head. Protrusion of eye.	3 years.	Not noted.	Slightly irregular. Not enlarged.	It was about 6 years after the ligation of the internal carotid artery before this patient became entirely well.
Surgical No. 42514.	48	Intracranial.	Fracture base of skull.	Headache and noise in head, exophthalmos.	13 months.	"Tortuous." Dilatation not noted.	Normal.	
Surgical No. 45360.	55	Intracranial.	Fracture base of skull.	Headache and noise in head, exophthalmos.	2½ months.	Not dilated.	Normal.	
Surgical No. 18104.	31	Occipital vessels.	Injury to head.	Swelling and noise.	7 years.	Not noted.	Not noted.	
Surgical No. 28688.	18	Neck.	Congenital.	Noise in head, dizziness, swelling.	18 years.	Proximal dilatation.	Not enlarged.	
Surgical No. 46583.	18	Neck.	Congenital.	Swelling and disability.	5 years.	Undetermined.	Normal.	

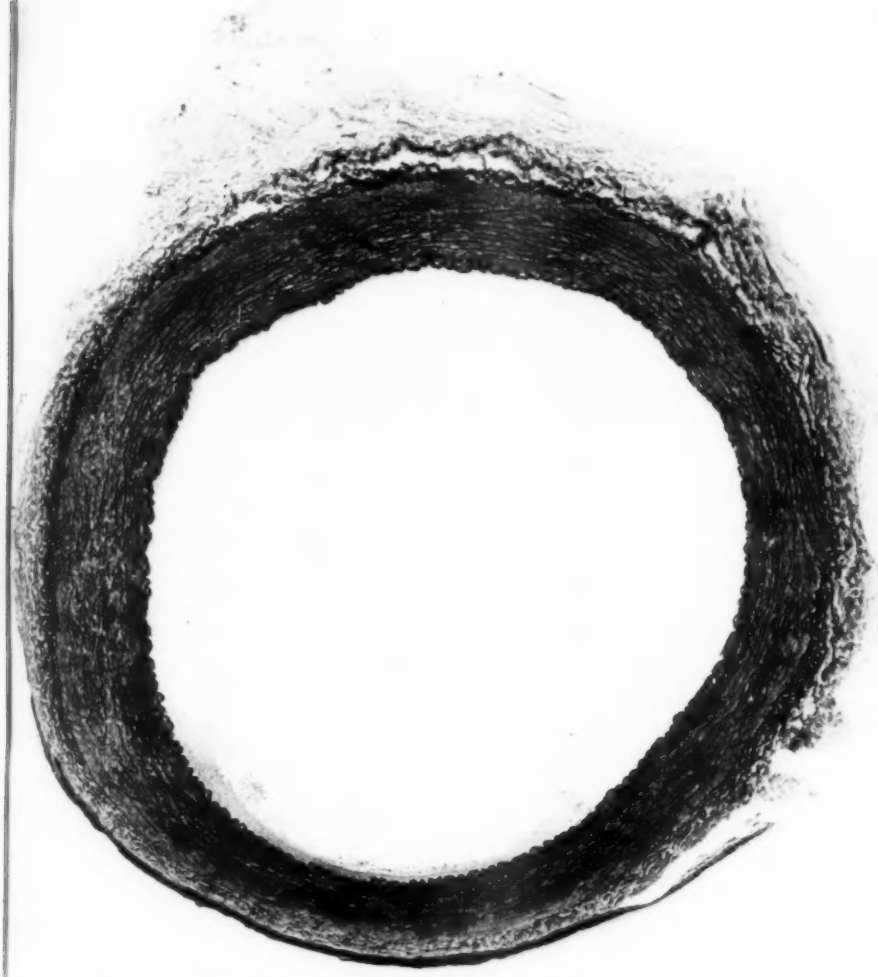

FIG. 11.—Dog 9. Photomicrograph of artery proximal to fistula. Magnified 41 times. Weigert's elastic tissue stain. Elastic tissue is not as prominent as in Fig. 12. Note the areas of apparent scarring in the wall.

FIG. 12.—Dog 9. Photomicrograph of artery distal to fistula. Magnified 41 times. It is a little smaller than the normal artery of the left side. The elastic tissue is coarse and prominent.

FIG. 13.—Dog 9. Photomicrograph of normal carotid artery of the left side. Magnified 41 times.

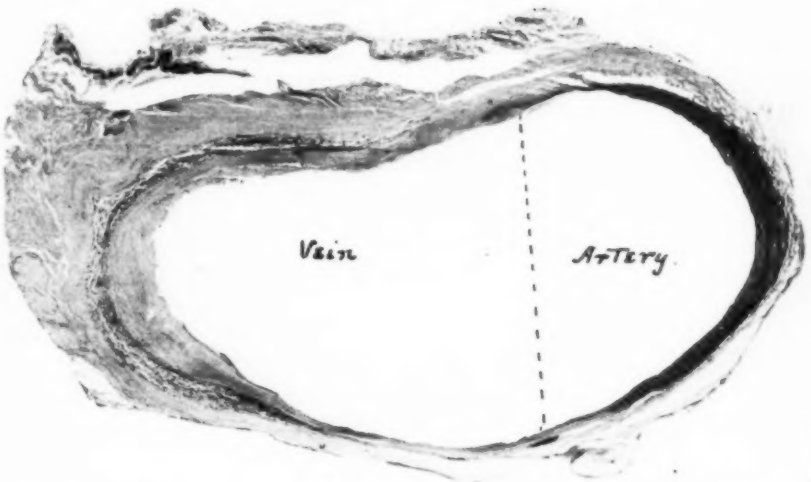

FIG. 14.—Dog 9. Photomicrograph of section through fistula, showing vein and artery. Magnified 15 times. Duration of fistula 32 months. Note the elastic tissue of the vein.

FIG. 15.—Dog 9. Photomicrograph of vein proximal to the arteriovenous fistula. Magnified 20 times. Marked increase of elastic tissue.

FIG. 16.—Dog 9. Photomicrograph of vein distal to the fistula. Magnified 20 times. The elastic tissue is less marked than on the proximal side of the fistula.

FIG. 17.—Dog 9. Photomicrograph of external jugular vein of left side of the neck. Magnified 20 times. The vessel is also hypertrophied due to the collateral circulation with the opposite vein.

FIG. 18.—Case 3. Photomicrograph of artery and vein proximal to the fistula. Magnified 4⅔ times. The hypertrophied wall of the vein is evident.

FIG. 19.—Case 3. Photomicrograph through vessels at point of fistula, showing the aneurysm which developed in the artery opposite the fistula. Magnified 4⅔ times.

FIG. 20.—Case 3. Photomicrograph of artery and vein distal to the fistula. Magnified 4⅔ times. Hypertrophy of vein less marked than in Fig. 18.

closed by means of a thin septum of fibrous tissue lined on both sides by intima, while the lumina of the vessels remained undisturbed. Thrombosis, without infection, did not occur. In the femoral region the vessels lie in very close apposition, whereas in the neck the external jugular vein is widely separated from the internal carotid artery. It may be that when there is angulation at the point of fistula the blood-stream flows more directly through it, and thus tends to keep the fistula from closing. It is probable that the spontaneous closure in this series of experiments was due to the small vessels, and consequently the necessarily small fistulæ, yet to me it will be very interesting to learn if many traumatic fistulæ, the result of the late war, close without operative interference. The presence of the thrill and the characteristic bruit are sufficient to permit the diagnosis even when there are no other signs nor symptoms.

In a few of our cases of arteriovenous fistula (Cases 1, 2 and 3) the heart was noted to be enlarged and irregular in its action. But we could not prove that this abnormality of the heart was coincident with, or due to, the fistula. With this point in view, Dog 9 permitted some interesting observations which would indicate that an arteriovenous fistula in the neck of a dog does cause marked cardiac disturbance. Before death this dog's heart became very much enlarged, irregular in action and developed a marked systolic murmur, which was present over the entire precordium and was transmitted to the axilla and back. In the absence of any other cause for death, I am inclined to believe that this animal died of cardiac failure. An X-ray of Dog 9's heart was made 20 months after the production of the fistula, and again at the end of 32 months. In this period of a year the heart had increased markedly in size (Figs. 4 and 5). It is to be regretted that no X-rays were made before the fistula was produced. For purposes of comparison I am publishing a roentgenogram (Fig. 3) of the heart of a normal dog which weighed 17¼ pounds, or 3 pounds more than Dog 9 weighed. If you suppose this to represent the size of the heart of Dog 9 before the fistula was produced, the marked increase in the size of its heart during the first 20 months that the fistula was present can be seen by comparing the picture with Fig. 4. Electrocardiograms of Dog 9 were made on the same days that the X-rays were taken (Figs. 1 and 2). Dr. E. B. Bridgman has very kindly commented upon these electrocardiograms for me. "Several features appear on comparison of these two tracings taken with the same standardization of current. There have been obvious changes in the pictures as shown by (1), an inversion of T_1, (2), a relative increase in the height of T_2 and T_3; (3), the appearance of Q_1, (4), the disappearance of S_1 and (5), a relative change in the sequence of deviations as manifested by the R waves. There has been no prolongation of PR time, and the marked degree of sinus arhythmia is characteristic of the normal tracings of the dog's electrocardiograms. The differences suggest myocardial changes and, perhaps, a relative hypertrophy of the right ventricle." Further convincing proof of the cardiac hypertrophy was furnished by the autopsy. The heart was markedly hypertrophied, weighing 160 gm. In a series of normal dogs,[6] whose average weight was 27 pounds, the average heart weight was 145 gm. Dog 9 weighed only about half as much as was the average weight of this series, yet its heart was 15 gm. heavier. Microscopically the heart muscle showed the typical picture of cardiac hypertrophy. There was no evidence of chronic myocarditis.

Below a partially constricting aluminum band there are definite changes in the blood pressures and the structure of the vessel wall. The systolic pressure is reduced, while the diastolic pressure is increased, thus lowering markedly the pulse pressure. There is also a definite atrophy or partial disappearance of the elastic tissue in the vessel wall for a short distance below the band. These changes probably play an important part in causing the dilatation. Do the same conditions exist in the dilated artery proximal to an arteriovenous fistula? End pressures obviously cannot be taken, for in so doing the effect of the fistula on the proximal blood pressures would be eliminated. Pressures obtained through a needle introduced into the lumen of the vessel seem plausible, and experiments to determine this point are now in progress. In the dilated artery the amount of elastic tissue is less than in the artery just distal to the fistula. Owing to the dilatation, this change of elastic tissue may be more apparent than real. The histological structure of the artery distal to the fistula seems to be the same as that of the normal vessel in the opposite side of the neck. The effect of the fistula on the walls of the artery and vein is shown in the photomicrographs (Plates XXIII and XXIV).

A study of the clinical cases reveals that the artery was observed to be dilated proximal to the fistula in five instances. In seven of the cases the histories do not comment on the size of the artery. In one case in which the fistula had been present for only three months, the artery was not dilated. In Case 14 a dilatation of the innominate artery was not determined, as it was not exposed. It is interesting to note that those patients in whose history no mention is made of the size of the artery, the arteriovenous fistula was intracranial in three, in the hand in two, between the occipital vessels in one, and in the femoral region in one. In intracranial cases the surgeon has no opportunity to compare the artery proximal to the fistula with the artery distal to it, or with the normal carotid artery on the other side. This seems to me the most plausible explanation why proximal dilatation of the artery has not been noted in cases of intracranial arteriovenous fistula. Also, the duration of the fistula is usually short, as the severe symptoms drive these patients to seek aid soon after the fistula is produced. The size of the vessels involved in an arteriovenous fistula and their distance from the heart may influence the proximal arterial dilatation. In the two hand cases in which the fistula had been present for 10 and 20 years, respectively, the dilatation would probably have been noted if it had been very evident. All of the femoral arteriovenous fistulæ, except the two of three and four months' duration, resulted in a proximal dilatation of the artery.

[6] Reid, Mont R.: "Ureterovenous anastomosis," The Johns Hopkins Hosp. Bull., Balto., 1918, XXIX, 55.

The dilatation of the artery in cases of arteriovenous fistula seems to vary directly with the duration of the fistula. The process must be very slow and gradual. Clinically it is rarely noted in the first year. Experimentally, and by means of careful measurements of the vessels, I was able to detect a proximal dilatation in two cases of four months' duration (Fig. 10).

This experimental and clinical study convinces me that grave cardiac disturbances may result from the presence of an arteriovenous fistula. Cardiac hypertrophy and dilatation due to this cause are scarcely mentioned in the medical literature. The heart of Dog 9 was markedly enlarged and death was probably due to cardiac insufficiency. In three of the clinical cases the heart was markedly enlarged, and in one case the cardiac condition was so bad that surgical treatment of the fistula was not attempted. In the absence of other causes to explain the cardiac hypertrophy in these cases is it not reasonable, in the light of the observations on Dog 9, to assume that the arteriovenous fistulæ may have been responsible? It may be that the proximal dilatation extends gradually all of the way to the heart. Cases 1 and 2, and Dog 9 would seem to indicate such an extensive process. In Case 5 the heart was not enlarged, and the proximal arterial dilatation did not extend to the aorta. The cardiac disturbances may not begin until the arterial change becomes extensive.

In this connection it is interesting to note that in two patients with congenital arteriovenous fistula in the neck, both aged 18 years, there was no apparent abnormality of the heart, although in one case there was a definite proximal dilatation of the artery. The adaptation of the heart to congenital vascular anomalies may be so gradual that there is no demand for an abnormal hypertrophy and dilatation. Persistent ductus arteriosus, congenital arteriovenous fistula, pulsating naevi and patent septa of the heart may frequently be unassociated with an abnormal function or size of the heart, whereas the acquirement of these conditions after the heart has become adapted to one normal state might lead to marked, but necessary, compensatory changes. A heart that works for a congenital abnormality may not recognize it as such.

If an arteriovenous fistula will cause cardiac hypertrophy, then it seems that we may have a means of throwing some light upon the complex problem of cardiac hypertrophy. Is it due to a mechanical effect of the fistula upon the heart? May blood pressure changes be responsible for the dilatation of the heart as well as the artery? Does an increased vascular bed cause cardiac hypertrophy? Or is it nature's adaptive response to the demand of a given part for better circulation? Many other such questions could probably be studied in connection with experimental arteriovenous fistula.

SUMMARY

1. An arteriovenous fistula of long duration usually causes dilatation of the artery proximal to the fistula. This dilatation may extend as far as the heart.

2. Marked cardiac disturbances may result from an acquired arteriovenous fistula of long standing. They are hypertrophy and dilatation with eventual cardiac decompensation.

3. The wall of the vein involved in an arteriovenous fistula becomes hypertrophied. Although the vein on the proximal side of the fistula does not increase markedly in size, its wall shows a greater increase of elastic tissue than the wall of the vein distal to the fistula.

4. The venous blood pressure is increased in the part of the body distal to an arteriovenous fistula. When the fistula is cured the pressure returns to normal.

THE BIOLOGICAL CLASSIFICATION OF INFLUENZA BACILLI

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Since the discovery of *B. influenzæ* medical literature has become burdened with discussions about its relationship to epidemic and sporadic influenza, pneumonia, pertussis, diphtheria, measles, scarlet fever, conjunctivitis, and meningitis, whether it is really hemoglobinophilic, and whether all strains are alike morphologically, culturally and immunologically. It is very interesting reading, but, after all, the answer to many questions seems no nearer than it was almost 30 years ago. A brief review is necessary to show the exact status of *B. influenzæ* and the difficulties presented in undertaking a study of this kind.

Pfeiffer[1] described a small Gram-negative bacillus in smears from the pharynx and the sputum of influenza patients. Later he cultivated the bacillus, finding hemoglobin essential for its growth on artificial media, and further characterized it as non-motile, aërobic, not found in the blood of influenza patients, and not very pathogenic for animals. Afterwards he found in three cases of bronchopneumonia following diphtheria in children a bacillus in every respect the same as the one spoken of as the true influenza bacillus, with the exception that it was larger and developed many thread-like forms. This organism he called the pseudo-influenza bacillus. The differentiation was made on morphology alone. Wolff,[2] in 1903 stated that Pfeiffer believed all influenza bacilli were the same, and that his original idea of a pseudo-influenza bacillus was incorrect.

Cantani[3] thought that the pseudo-influenza bacillus and the true one were identical, and that neither of them were hemoglobinophilic, as they could be grown on media, enriched with spermatic fluid, which did not give the spectroscopic band of hemoglobin. Ghon and Preyss[4] considered hemoglobin necessary even though it were present in such small quantities that

it failed to give a band with the spectroscope unless hydrazin were added. Neisser [5] was able to grow an influenza-like bacillus, isolated from a case of purulent conjunctivitis, on plain agar for 20 generations in symbiosis with a xerosis bacillus. Davis [6] thought hemoglobin, acting as a catalytic agent, was necessary for growth, and showed that a very small amount was required (1 part in 180,000 parts of medium). According to him, growth will take place in the presence of coagulated hemoglobin, but if the hemoglobin be broken up by excessive heating into hematin and globin, no growth occurs.

The difficulties which arise in the exact identification of an influenza bacillus have caused many mistakes in the past and probably will continue to cause them. Spengler,[7] Luzzatto[8] and Jochmann and Krause [9] have described at different times a bacillus which they considered the cause of pertussis. It is now believed they were dealing with the group of influenza bacilli and not the organism later described by Bordet and Gengou.

Gram-negative hemoglobinophilic bacilli have been recovered from different parts of the human body, also from animals, under a variety of conditions. Rosenthal [10] considered them ordinary members of the mouth flora without pathogenic significance. Auerbach,[11] Davis,[12] and many others have isolated them from the throats of patients with measles, pertussis, diphtheria and scarlet fever. Klieneberger [13] described a pseudo-influenza bacillus which he isolated from pus in a gall-bladder. Cohn [14] recovered *B. influenzæ* from a case of acute urethritis. It is generally known that these organisms may cause sinusitis, pneumonia, septicemia, endocarditis, arthritis, otitis media, and meningitis. Davis [15] isolated from the urine of three patients a small, Gram-negative, hemolytic, anaërobic, hemoglobinophilic bacillus. Moon [16] recovered a small, Gram-negative anaërobic, hemoglobinophilic bacillus from a chronic ethmoid infection. Friedberger,[17] working in Pfeiffer's clinic, isolated from the preputial secretions of a dog a small, Gram-negative, non-motile, hemoglobinophilic bacillus. Wolff,[2] working in the same clinic, isolated from the lungs of a rat a bacillus that remained exactly like *B. influenzæ* for three months, after which time it acquired the property of growing on ordinary media. Pritchett and Stillman [18] have recovered from throat cultures a Gram-negative, non-motile, aërobic, hemolytic, hemoglobinophilic bacillus which makes milk alkaline (growth takes place when a little blood is added to the milk).

In 1905 Wollstein,[19] working on pertussis, isolated bacilli considered as belonging to the influenza group, but from which they could be differentiated by agglutination and absorption tests. In 1906,[20] not feeling so positive about this difference, she says: "The similarity of cultural characteristics of all the influenza bacilli has been emphasized by Neisser, and my experience with the agglutination reactions leads me to regard all strains as belonging to one family."

Meunier [21] (1897) reported 10 cases of broncho-pneumonia in young children caused by *B. influenzæ*. In several instances the bacillus was recovered from the blood both before and after death. At this time, contrary to Pfeiffer's statement, it was noted that these organisms were highly pathogenic for rabbits. Slawyk,[22] in 1899, isolated an influenza bacillus from the blood and spinal fluid of a child with meningitis. This organism was seen by Pfeiffer who agreed that it was *B. influenzæ*. Cohen [23] (1909) recovered from the spinal fluid and blood of patients with meningitis an organism similar to the influenza bacillus, except that it caused septicemia in rabbits, and because of this difference and evidence obtained by protection experiments, he was inclined to believe that the two organisms were not the same. Thursfield,[24] in 1910, reported two cases of *B. influenzæ* septicemia without meningitis. He agreed with Cohen and concluded by saying, "Organisms hitherto described as *B. influenzæ* are not all identical, but like the coli-typhoid family, belong to a group the various members of which possess very different pathogenic powers." Wollstein,[25] in 1911, working with respiratory and meningeal strains, considered them identical, and varying only in virulence. Davis,[26] in 1911, found no difference in the virulence of respiratory and meningeal strains. Wollstein,[27] in 1915, still regarded all influenza bacilli as more or less identical regardless of their own origin or virulence. Davis,[15] in 1915, suggested dividing them into two groups, one showing the phenomenon of symbiosis, the other lacking it. Williams,[28] in 1919, working with a number of strains reported a few crosses by agglutination, but none by absorption tests. Huntoon and Hannum,[29] in 1919, say, "We have found no strains among our collection which do not show relationship either directly or indirectly through absorptions." Gay and Harris,[30] in 1919, found in their serological work on influenza evidence that influenza bacilli probably could be divided into groups.

In spite of the vast amount of work done, very little is known about *B. influenzæ* and its biological activities. At present it is described as a small, Gram-negative, aërobic, non-motile, hemoglobinophilic bacillus. For all that is known, there may be a number of different kinds of bacilli answering that description, or there may be only one. In reality there is one true *B. influenzæ* existing in name only, and that is the first one grown and described by Pfeiffer, as he did not and could not prove any of the subsequent strains to be identical with the first.

Jordan [31] has made the best contribution lately to our knowledge of influenza bacilli by showing that 10 of 13 strains formed indol. Owing to this discovery a study of the cultural characteristics of different strains of *B. influenzæ* was undertaken. The work has not been completed, and what follows is merely a preliminary report made at this time with the hope that others will become interested and assist in the solution of the problem.

The bacilli for study were obtained from normal throats since the epidemic, 32 strains; from influenza meningitis, 5 strains (4 coming from Dr. Howland's clinic this year and 1 isolated by Dr. Wollstein in 1917); and from cases of epidemic influenza, 14 strains (supplied by Drs. Parker, Wollstein and Stillman). Two strains of *B. pertussis*, one from Dr. W. W. Ford, the other from the N. Y. Board of Health

were studied at the same time for comparison. In isolating the organisms from normal throats, all Gram-negative, aërobic, hemoglobinophilic bacilli were included in the series regardless of morphology and the kind of colony formed, since these latter vary so much under different conditions that they are unreliable criteria.

In a study of this kind it is necessary to be able to obtain at all times a vigorous growth of the organisms both on solid and in liquid media and describe their colony formation, morphology and biological activities under as favorable conditions as possible. Meat-infusion agar and broth, Ph 7.5, with from 1 to 2 per cent rabbit blood, furnish good mĕdia for growth and to which other ingredients may be added for study.

All the strain are hemoglobinophilic after at least two months of artificial cultivation, except in a few instances, in which they were grown on hemoglobin-free media in symbiosis with other bacteria for several generations. They are Gram-negative, non-motile, do not liquefy blood-gelatin, do not ferment glucose, lactose, saccharose, maltose, mannite, salicin, inulin, glycerol and xylose in one week, and, most of them, including the three hemolytic ones, have at some time shown the phenomenon of symbiosis. Three strains hemolyse rabbit blood both in liquid and in solid media.

In working with the morphology and colony formation, it is necessary to grow the various strains side by side, generation after generation, on exactly the same medium, and then it is possible to notice in a general way differences between them. Fig. 1 (magnification 8) shows colonies of four different organisms 36 hours old, grown under the conditions named above, the upper row as seen by direct light, the lower by top light. No. 1 forms indol, No. 2 forms amylase, No. 3 is hemolytic, No. 4 is *B. pertussis*. Nos. 1 and 3 are moist, become very granular and dark in the center, and when one to five days old put out daughter colonies. No. 2 is tough, holds its shape, and puts out very few daughter colonies. All pit and turn the medium a dirty brownish color. All are tan-colored after 48 hours. Older observers attributed this color to the hemoglobin in the medium, but this is unlikely as it occurs when they are grown on hemoglobin-free media in symbiosis with other bacteria. Figs. 2 and 3 (magnification 20) are copies from Pfeiffer[1] and Grassberger[32] showing the type of colonies with which they were working.

When a solid medium is inoculated with the various strains, there is seen a distinct and constant difference between the edges formed. Cultures of *B. pertussis* (Fig. 4) have elevated, smooth edges; some of the influenza bacilli (Figs. 5 and 6), elevated, lobate edges; others (Figs. 7 and 8), slightly elevated, finely irregular edges; and others which grow very delicately have no sharply defined edges. (See lower right corner of Fig. 9 which also shows two other types of cultures mentioned above, and finally *B. pertussis* in the upper right corner). Smears from cultures with the lobate edges usually show the typical small bipolar-staining bacilli called the true influenza bacillus, whereas smears from the ones with finely irregular edges and no sharply defined edges usually show large, more easily stained bacilli, bizarre shapes, and thread-like forms. This difference is well shown by copies of Pfeiffer's[1] true (Fig. 10) and his pseudo-influenza (Fig. 11) bacilli.

One of the first things noticed when working with influenza bacilli was that some strains both on solid and in liquid media soon developed a perfectly characteristic fresh fecal odor. Later, when cultures of the different strains were tested for indol formation, it was found that the ones which produced this odor gave positive tests for indol when the ether extracts were layered with Ehrlich's reagent. Cultures have been distilled and ether extracts of the water-clear distillate gave the same results as were obtained before distillation. Repeated tests have been made on the various strains grown from two days to two weeks, and indol has been produced constantly by some, and not, just as constantly, by others. Thirty of the 51 strains form indol and the five meningeal ones are in the positive group. The spinal fluids of patients with influenza meningitis do not give a positive test when first drawn, but, if a tube of it be placed in an incubator for from 12 to 24 hours, a definite test is obtained. The fluid from a meningococcus meningitis gave a negative test when thus treated.

The ability of the various influenza bacilli to form amylase has been studied in the following manner. Defibrinated rabbit blood was added to melted meat-infusion agar which was kept at 95° C. long enough to destroy the amylase present in the blood. Then to 100 c. c. of this mixture were added from 10 to 15 c. c. of a 2 per cent sterile soluble starch solution. Plates were poured, allowed to cool and inoculated at various points with different influenza bacilli, and after from 3 to 5 days incubations were covered with a weak Lugol's solution. If the starch were not split, the medium was a dark blue up to the edge of the cultures, but if it were changed, the iodine reaction was absent around them, a colorless zone of from 4 to 8 mm. in width being left. A positive and a negative reaction are shown in Fig. 12. Nine strains produce amylase in small amounts, and none of these produce indol.

Tubes of potassium nitrate blood-broth were inoculated with influenza bacilli, incubated for 5 days, and then tested with the sulphanilic acid and naphthylamin reagent for nitrites. Thirty-three of the 51 strains have at some time given a positive reaction. Some always reduce the nitrates, others do so irregularly, while still others have never done so. This characteristic is displayed by some indol formers, by some amylase formers and by two of the three hemolytic ones. Further work may show that all can reduce nitrates under the proper conditions, making this a common characteristic of the whole group, just as hemoglobin is essential for their growth.

Flasks of 100 c. c. of fat-free milk with brom-cresol purple for an indicator, and flasks of 100 c. c. meat-infusion broth with the same indicator were autoclaved separately. (If autoclaved together a precipitate forms which interferes.) After cooling, equal quantities of the milk and the broth were mixed and from 1 to 2 per cent rabbit blood was added. This is a good medium for the growth of influenza bacilli, and accurate readings can be made when an uninoculated tube is

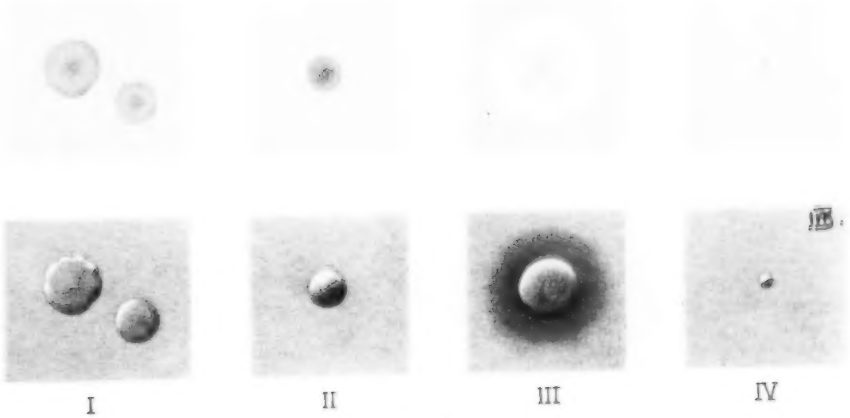

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 12.

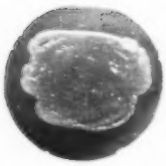

FIG. 4.

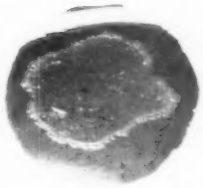

FIG. 5.

FIG. 6.

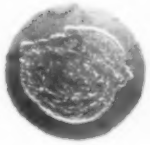

FIG. 7.

FIG. 8.

FIG. 9.

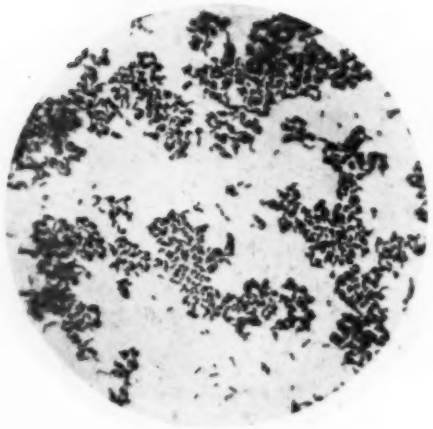

FIG. 10.

FIG. 11.

kept for a control. When these tubes of blood-broth-milk were inoculated and incubated, it was obvious very soon that all influenza bacilli are not the same culturally, as some, within 48 hours, made the milk slightly but definitely acid, others slightly but definitely alkaline, while still others gave doubtful results. This difference persisted for a week. Readings made at intervals longer than a week cannot be given at this time. The source of the acid is unknown, since lactose is not fermented.

DISCUSSION

Many people have never felt absolutely certain that the differences between *B. pertussis* and *B. influenzæ* were sharp enough to be beyond doubt in spite of the serological proof. *B. pertussis*, after a period of artificial cultivation, can be grown on plain media, forms no indol, no nitrites and makes milk very alkaline. Some of the influenza bacilli also form no indol and no nitrites, but none of them has ever made milk nearly as alkaline as *B. pertussis*.

Time alone will tell whether these cultural characteristics will be constant. While there are differences in the biological activities of the various strains of *B. influenzæ*, at the same time there are definite groups, the individual members of which are similar culturally. Only one group will be discussed at this time. It consists of 10 strains five from the spinal fluid of patients with influenza meningitis, two epidemic strains from New York, and three from normal throats. The growth and morphology of these are similar, all from indol, all reduce nitrates to nitrites, and make blood-broth-milk slightly acid within 48 hours.

Whether the strains of large bacilli that are amylase formers, or the hemolytic ones, should be included in this big influenza group is a question that will have to be decided. The nine amylase formers and the three hemolytic strains have characteristics in common with the big group, as shown by certain ones forming nitrites and by one of the hemolytic strains forming both indol and nitrites. Possibly this is a big group of organisms, like the streptococci, which have been divided into hemolytic and non-hemolytic strains, and further subdivided by cultural characteristics and serological tests. Possibly the group can be compared with the Gram-negative diplococci, Meningococcus, Parameningococci, Micrococcus catarrhalis, Micrococcus flavus, Micrococcus pharyngis siccus, Gonococcus and others.

CONCLUSIONS

1. The Gram-negative, non-motile, hemoglobinophilic bacilli can be classified biologically by reactions which admit of subdivisions of the group.

2. In working with a suspected *B. influenzæ*, the following routine should be followed:

(a) Determination of hemoglobinophilic qualities.
(b) Colony formation.
(c) Hemolytic test.
(d) Gram stain.
(e) Morphology.
(f) Motility.
(g) Indol formation.
(h) Reduction of nitrates to nitrites.
(i) Amylase formation.
(j) Reaction in blood-broth-milk.

3. *B. pertussis* can be differentiated from the group of *B. influenzæ* by cultural characteristics.

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